HEALTH TECHNOLOGY ASSESSMENT REPORT

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INTEGRATED VECTOR MANAGEMENT FOR *AEDES* CONTROL

HEALTH TECHNOLOGY ASSESSMENT SECTION (MaHTAS)
MEDICAL DEVELOPMENT DIVISION
MINISTRY OF HEALTH

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EXECUTIVE SUMMARY

Background

Aedes aegypti, a cosmotropical mosquito that thrives in urban environment, is a vector of international concern. It transmits to humans important arboviral diseases; dengue, yellow fever, zika and chikungunya causing considerable morbidity, mortality and healthcare expenditure in low and middle-income countries. Dengue is the most important arboviral disease globally and the fastest emerging arboviral infection posing a major public health concern throughout tropical and subtropical region in the world. It is the most rapidly spreading mosquito-borne viral disease, with a 30-fold increase in global incidence over the past 50 years and is endemic in more than 100 countries.While dengue is a global concern, currently close to 75% of the global population exposed to dengue reside in Asia Pacific. The global increase of dengue incidence is also experienced by Malaysia with reported incidence of 30.2 cases per 100,000 population (2000) to 261.6 cases per 100,000 population (2017). Dengue has high social and economic impact, affecting not just the patient, but also families, health services and the community. In the Americas, an estimated economic cost of the disease was in excess of US$2.1billion per year. In Malaysia, an estimated US$73.5million in public funds or 0.03% of the country's GDP was spent on its National Dengue Vector Control Programme, which represented US$1,591 per reported dengue case (2010).[13]

The control of vector-borne diseases is one of the greatest challenges on the global health agenda. Various strategies for vector control exists and have been used for decades, using chemical, physical, biological, or an integrated approach. Dichlorodiphenyltrichloroethane (DDT) was one of the first chemical measures used to target adult dengue vectors. Subsequent DDT resistance led to dengue re-emergence followed by introduction of second and third generation insecticides. Alternative methods consist of biological control, release of transgenic vectors and environmental management were introduced. Factors influencing the transmission of dengue such as the virus, the human as the host, the vectors, unsatisfactory environmental condition and climate change, with rapid urbanisation, population growth and international travel, creates challenge in the efficient control of the disease. Integrated Management Strategy for the Prevention and Control of Dengue (IMS-Dengue) as highlighted by World Health Organisation (WHO) consisted of strengthening epidemiological surveillance, laboratory networks, integrated vector management (IVM), clinical management of patients, environmental management and social communications. The Global Strategic Framework for IVM identifies five key elements for its successful implementation. Integrated vector management comprises two or more strategies employed simultaneously.[4] In Malaysia, IVM for Dengue prevention and control has been implemented with these strategies:- [22]

- Reprioritising *Aedes* surveillance areas
- Strengthening information system for effective disease surveillance and response, the Communicable Disease Control Information System
- Legislative changes
- Community participation and intersectoral collaboration - national cleanliness and antimosquito campaigns

- Changing insecticide fogging formulation from malathion to water-based pyrethroid (resigen and aqua resigen) and mass abating using Abate

Despite decades of control programme, mosquito population is still abundant and dengue incidence persists with outbreaks occuring in affected communities worldwide. Besides, it was said that there was no evidence that vector-control efforts such as massive use of insecticides have significant effect on dengue transmission. Thus, the need for evidence-based selection of the most appropriate, cost-effective and environmentally save interventions for *Aedes* control has never been greater. Therefore, the purpose of this Health Technology Assessment (HTA) is to evaluate the evidence of effectiveness, safety and cost-effectiveness, organisational, social and ethical implications of IVM for *Aedes* control in Malaysia. This assessment was requested by the Head of Vector Borne Disease Sector, Disease Control Division, Ministry of Health.

Technical features

Integrated vector management (IVM) is defined as a rational decision-making process for the optimal use of resources for vector control, aiming to improve efficacy, cost-effectiveness, ecological soundness and sustainability of disease-vector control with ultimate goal to prevent vector-borne diseases transmission including dengue. It is part of a comprehensive strategy encompassing a variety of other vector control methods such as collaboration with the health sector and other sectors, educational campaigns, advocacy, social mobilisation, evidence based decision making and capacity building. This strategic framework, adopted in 2004 for all vector-borne diseases is a rational decision making process for the optimal use of resources for vector control. The ultimate goal is to prevent the transmission of vector-borne diseases such as malaria, dengue, Japanese Encephalitis and Chagas disease. The Global Strategic Framework for IVM identifies five key elements for the successful implementation of IVM:-

- Integrated approach
- Evidence-based decision making
- Advocacy, social mobilisation and legislation
- Collaboration within the health sector and with other sectors
- Capacity building

Effective vector based dengue prevention involves initiating control measure such as source reduction and larvicide treatment before the beginning of vector season, and adult reduction measure following detection of human arbovirus activity. During outbreaks, a combination of containment and large scale vector control may be used to minimize vector-human contact. Vector surveillance is a key component of any local IVM programme. Data derived from the vector surveillance primarily estimates mosquito abundance, which is used to indicate level of risk. The indicators that are commonly used are: i) immature stage (larvae and pupae) survey indices, ii) eggs per ovitrap per week, iii) female mosquitoes per sticky gravid trap per week, and iv) adult infection rates. Mosquito threshold for disease transmission using larval and pupal indices should be determined by each local vector control programme.

Policy question

Which IVM strategies will be the most effective, safe and cost-effective approach for *Aedes* control in Malaysia?

Objectives

i. To determine the effectiveness of IVM for *Aedes* control compared with no comparator or other control measures
ii. To determine the safety of IVM for *Aedes* control compared with no comparator or other control measures
iii. To determine the economic, social, organizational, ethical and legal implications of IVM for *Aedes* control

Methods

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2019), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2019), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2019), EBM Reviews-Health Technology Assessment (1st Quarter 2019), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2019). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits were applied to the search. The last search was run on 30 March 2019. Additional articles were identified from reviewing the references of retrieved articles. One of the tools used to assess the risk of bias and methodological quality of all the articles retrieved is the Critical Appraisal Skills Programme (CASP) checklist. All full text articles were then graded based on guidelines from the U.S./Canadian Preventive Services Task Force.

Results and conclusion

Nineteen (19) full text articles were finally selected for this review which comprised of of five systematic review with/without meta analysis, three cluster RCTs, one cohort study, four pre-post intervention studies, one cross sectional study, three cost-effectiveness analysis and two cost analysis.Of the 19 included articles, twelve studies were included in the effectiveness section in this review. The other five studies were related to cost-effectiveness of IVM for *Aedes* control and two on social aspect of IVM for *Aedes* control.The included articles were published between 2006 and 2017. Most of the studies were conducted in Brazil and Thailand, followed by Mexico, Cuba and UK (two studies), and one study each from Argentina, Canada, Australia, Malaysia and Switzerland. This review included altogether a total of 814,149 residents from all the studies, involving 194,797 households. Sample size for each of the included studies ranged from 1800 to 470,000 subjects. The longest follow-up of the included study was up to ten years. Most of the study participants were residents in urban and peri urban dengue transmission areas as well as students.

Effectiveness

There was fair level of retrievable evidence on effectiveness of IVM for Aedes control.

Combination of larviciding and community based strategy; combined community based environmental control and water container cover; as well as house screening reduced the rate of dengue incidence (RR=0.19, OR=0.22,OR=0.22) respectively.

Three entomological indices were widely used as outcome measures; the BI, CI and HI. With regard to BI, the pooled RE ranged from 0.24 (chemical control, outdoor adulticide) to 0.71(environmental management consisted of environmental modification, environmental manipulation, modification of human habitat or behaviour to reduce human-vector contact). Pooled RE for CI ranged from 0.17 (IVM; combination of EM and chemical control) to 0.43 (EM). Meanwhile, pooled RE for HI ranged from 0.12 (IVM; EM and chemical control) to 0.49 (EM). IVM (combination of EM and chemical control) was the most effective method to reduce the CI,HI, BI with the above results. Community participation was effective in reducing BI and CI, with pooled RD of -0.13, -0.03. Integrated Vector Management (EM and chemical control) had the largest number of population covered (median population size of 12,450; ranged from 210 to 9,600,000).

Eco-bio-social (integrated community based) intervention was effective in significantly reducing overall PPI values in intervention cluster (-85.1%) compared to control cluster (-47.2%, p<0.001).

Performance analysis of different control strategies showed all category of interventions (biological, chemical, integrated) contributed significantly to the control of *A aegypti* (p<0.0001), with integrated intervention demonstrated as the most effective method.

For sustainability of programme, the community-based strategy adopted in the studied community was rated as well-sustained, sustainability scores ranged from 4.20 to 4.42.

Safety

There was no retrievable evidence on the safety of IVM for *Aedes* control.

Cost-effectiveness

There was limited retrievable evidence on economic evaluation of IVM for *Aedes* control.

Evidence demonstrated there was variation in the ICER for different strategy; following community participation was $3952.84 per DALY avoided, using two applications of high-efficacy adult control was $615 per DALY saved; whereas ICER for the use of six applications of high-efficacy adult control was $1267 per DALY saved. The strategy using two applications of high-efficacy adult control per year was the most cost-effective (cost minimisation strategy), and using six applications of high-efficacy adult control per year was the most cost-effective (benefits maximisation strategy) . The community-based approach was more cost-effective compared to vertical programme from health system perspective (US$964 versus US$ 1406 per focus) as well as from society perspective (US$1508 versus US$1767 per focus).

The total economic cost per inhabitant per months increased from USD2.76 in months without transmission to USD6.05 during an outbreak for dengue control and management, equivalent to an increase in the average monthly cost from USD 673,959 (in month without transmission) to USD 1,477,617 (during an outbreak), amounted to 0.7% of the country's monthly GDP in period without transmission to 1.5% in the period with transmission.

Malaysia spent an estimated US$73.5 million (95%CI US$million 62.0, 86.3) for the national dengue vector control, constituting 0.03% of the country's GDP in 2010 (US$247.5billion), 92.2% of these costs were incurred at District Health Department level, human resources costs made up 64.8% of total national vector control costs while pesticide, fogging equipment, PPE, and outsourced fogging activity made up 19.4% of the total national vector control cost.

Financial implication

In Malaysia, over three years (2016 to 2018), the proportion of total cost saving from reduction of dengue cases (MYR 101million) relative to total cost of integrated dengue vector control (MYR 772 million) was approximately 13.08%.

There was also minimal reduction (15.07%) in cost-related to dengue illness (MYR 101 million) relative to the estimated annual economic burden of dengue illness demonstrated over three years (MYR 670 million).

As of 8th May 2019, the total dengue cases reported was 45,660. Therefore, estimated total cost of dengue illness is MYR 116 million (May 2019), and MYR 348 million (December 2019), with the cost of vector control in 2019 estimated to remain as in 2018 (MYR 260 million).

Social

There was fair level of retrievable evidence on social implications of IVM for Aedes control.

Following integrated eco-bio-social intervention, higher percentage of people in the treatment clusters agreed that applying *copepods* and *Bti* to water-holding containers was not complicated, compared to the control clusters (67.1% vs. 52.1%, p=0.006). The percentage of people in the treatment clusters who agreed that it was only health volunteers who were responsible for dengue prevention in the community was significantly lower than in the control clusters (12.9% vs. 26.1%, p=0.013).

The community centred ecosystem management resulted in better community knowledge, attitude and practices in dengue prevention, increased household and community participation, improved partnership including a variety of stakeholders with prospects for sustainability, vector control efforts refocused on environmental and health issues and increased community ownership on dengue vector management.

Organizational

Capacity building, in particular human resource development is a major prerequisite, because the IVM strategy requires skilled staff and adequate infrastructure at central and local levels. Core functions and essential competency required for IVM at central and local levels required are outlined in the core structure for training curricula on integrated vector management.

The IVM must be actively advocated and communicated to ensure continued support. The general public must be made aware of the strategy and participate in its implementation. Communications for reaching them should lead to behavioural change and empowerment.

The IVM requires collaboration of various agencies and community participation in assuring sustainability. To foster sustainability, interventions must focus on capacity building in the recipient community. Institutionalization is a key process on the path toward sustainability.Though it is challenging to involve the population in the control efforts, any measure adopted should be based more on community involvement than on vertical approaches.

Health services personnel should be able to interact effectively with residents, and have role as health promoters and evaluators, while undertaking entomological surveillance and vector control. Emphasizing communication and interpersonal communication may transmit more appropriate messages for behaviour modification.

Ethical

The approach to genetically modified (GM) vectors for disease control raises few intrinsic ethical issues. Important environmental and human health concerns need to be assessed before release of any GM vectors, as there are concerns over unknown long term effect in human and the ecosystem.

Legal

Within the European Union, legislation of mosquito control agent is implemented through the Biocidal Product Directive (BPD)(98/8/EG) and the Biocidal Product Regulation (EU) No.528/2012. In Malaysia, established legislations to cover the prevention and control of vector-borne diseases are; i) Destruction of Disease-Bearing Insect Act (DDBIA) 1975 (Act 154), ii) Prevention and Control of Infectious Disease Act 1988 (Act 342), and iii) Local Government Act 1976 (Act 171).

Recommendation

Based on the above review on IVM for *Aedes* control, strategies using combination of environmental management, chemical control and community based activities reduced entomological parameter and rate of dengue incidence. Community based activity has good social acceptance and contribute towards sustainability of IVM. Chemical control using six applications of high-efficacy adult control per year was the most cost-effective method (benefit maximisation strategy). Hence, the current IVM strategy for *Aedes* control may need to be further strengthened in its implementation.

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ABBREVIATIONS

AI	:	*Aedes* Index
BI	:	Breteau Index
Bti	:	*Bacillus thuringiensis israelensis*
CASP	:	Critical Appraisal Skills Programme
CDCIS	:	Communicable Disease Control Information System
CER	:	Cost effectiveness ratio
CI	:	Confidence Interval
CI	:	Container Index
cRCT	:	cluster randomised controlled trial
DALY	:	Disability adjusted life years
DDT	:	Dichlorodiphenyltrichloroethane
DESE	:	Elementary school-based dengue education programme
DHD	:	District Health Department
DHF	:	Dengue hemorrhagic fever
EFG	:	Eco-health friendly partner group
ELISA	:	Enzyme-linked immunosorbent assay (ELISA)
EM	:	Environmental management
FGD	:	Focus group discussion
FHD	:	Federal Health Department
GDP	:	Gross Dosmetic Product
GIS	:	Geographic Information System
HI	:	House Index
HTA	:	Health Technology Assessment
I^2	:	Heterogeneity
ICER	:	Incremental cost-effectiveness ratio
IEC	:	Information, education and communication
IgG	:	Immunoglobulin G
IgM	:	Immunoglobulin M
IIS	:	Integrated intervention strategy
IMS-DENGUE	:	Integrated Management Strategy for the Prevention and Control of Dengue
IVM	:	Integrated vector management
KAP	:	Knowledge, Attitude, Practice
MD	:	Mean difference
OR	:	Odds ratio
PPPI	:	Pupae per person index
RCT	:	randomised controlled trial
RE	:	Relative effectiveness
RR	:	Relative risk
SHD	:	State Health Department
Spp	:	species
ULV	:	Ultra-low-volume
VND	:	Vietnamese Dong
WHO	:	World Health Organization

HEALTH TECHNOLOGY ASSESSMENT
INTEGRATED VECTOR MANAGEMENT FOR *AEDES* CONTROL

1 BACKGROUND

Aedes aegypti, a cosmotropical mosquito that thrives in urban environment, is a vector of international concern as it transmits to humans important arboviral diseases; dengue, yellow fever, zika and chikungunya.[1-4] It is highly anthropophilic and can also breed in small amount of clear water. The success of *Aedes aegypti* is linked to its opportunistic and high adaptability to the peridomestic environment exploiting any stagnant water as its breeding habitat.[5] *Aedes albopictus*, was originally confined to Asia, but now has expanded its global range and contributed to the spread of chikungunya and dengue virus.[6] Four main diseases spread by *Aedes aegypti* and *Aedes albopictus*; dengue, yellow fever, chikungunya and zika cause considerable morbidity, mortality and healthcare expenditure in low and middle-income countries.[7]

The main disease is still dengue, with incidence grown dramatically around the world in recent decades.[8] Dengue is the most important arboviral disease globally and the fastest emerging arboviral infection posing a major public health concern throughout tropical and subtropical region in the world.[9] Today, the disease is endemic in more than 100 countries in five WHO regions; with the Americas, South-East Asia and Western Pacific regions being the most seriously affected. The number of cases from these three regions reported an increase from 2.2 million (2010) to 3.2 million (2015).[8] It is the most rapidly spreading mosquito-borne viral disease, with a 30-fold increase in global incidence over the past 50 years.[9] While dengue is a global concern, currently close to 75% of the global population exposed to dengue reside in Asia Pacific.[10] Its epidemiology is rapidly evolving with more than 50% of the world's population lives in regions at risk of the disease, and evidence points towards further geographical and numerical expansion.[11] The global increase of dengue incidence is also experienced by Malaysia with reported incidence of 30.2 cases per 100,000 population (2000) to 261.6 cases per 100,000 population (2017).[12]

Dengue has high social and economic impact, affecting not just the patient, but also families, health services and the community. In the Americas, an estimated economic cost of the disease supersedes US$2.1billion per year.[13] In Malaysia, an estimated US$73.5million in public funds or 0.03% of the country's GDP was spent on its National Dengue Vector Control Programme, which represented US$1,591 per reported dengue case (2010).[14]

The control of vector-borne diseases is one of the greatest challenges on the global health agenda.Various strategies for vector control exists and have been used for decades, using chemical, physical, biological, or an integrated approach.[15] Dichlorodiphenyltrichloroethane (DDT) was one of the first chemical measures used to target adult dengue vectors. Subsequent DDT resistance led to dengue re-emergence followed by introduction of second and third generation insecticides (e.g. malathion and pyrethroids).[16] The use of DDT is banned since 1998 in Malaysia.[17] Chemical control nevertheless has shortcomings, including environmental contamination, bioaccumulation of toxins, concerns on human toxicity and emergence of resistance to insecticides in target species.[18,19] Alternative methods consist of biological control (e.g. the introduction of larvivorous organisms such as fish, copepods and insect larvae into water containers), release of transgenic vectors (aimed at reducing or even replacing the wild-type vector population with one that has a reduced capacity to transmit and reproduce) and environmental management (e.g. source reduction, provision of safe water, covering and screening of water containers, and reduction of human-vector contact by screening doors and windows and using insecticide-treated nets) were introduced.[20] Factors influencing the transmission of dengue such as the virus, the human as the host, the vectors, unsatisfactory environmental condition and climate change, rapid urbanisation, population growth and international travel, creates challenges in the efficient control of the disease. Integrated Management Strategy for the Prevention and Control of Dengue (IMS-Dengue) as highlighted by World Health Organisation (WHO) consisted of strengthening epidemiological surveillance, laboratory networks, integrated vector management (IVM), clinical management of patients, environmental management and social communications.[21] World Health Organisation promotes the strategic approach known as IVM to control mosquito vectors. Integrated vector management (IVM) is defined as a rational decision-making process for the optimal use of resources for vector control, aiming to improve efficacy, cost-effectiveness, ecological soundness and sustainability of disease-vector control with ultimate goal to prevent vector-borne diseases transmission including dengue. The Global Strategic Framework for IVM identifies five key elements for its successful implementation:-[22]

- Integration of non-chemical and chemical vector control methods, and integration with other disease control measures
- Evidence-based decision making guided by operational research and entomological and epidemiological surveillance and evaluation
- Advocacy, social mobilisation, regulatory control for public health and empowerment of communities
- Collaboration within the health sector and with other sectors through the optimal use of resources, planning, monitoring and decision-making
- Development of adequate human resources, training and career structures at national and local level to promote capacity building and manage IVM programmes

Integrated vector management comprises two or more strategies employed simultaneously.[4] Some forms of IVM, including chemical control, community involvement, and co-operation between services have been said as among the effective approach to reduce *Aedes aegypti* infestation or control dengue outbreaks.[20]

In Malaysia, IVM for Dengue prevention and control has been implemented with these strategies:- [23]

- **Reprioritising *Aedes* surveillance areas**
  Prior to 1998, *Aedes* larval surveys were concentrated in residential areas though *Aedes* breeding was demonstrated to be low, at around or below 1% of houses inspected. In contrast, surveillance at construction sites indicated *Aedes* index to be very high. Thus, in 1998, the approach was changed where vector control teams carried out regular inspections at construction sites, factories, abandoned housing projects, garbage dump sites, schools, government facilities and others, besides inspections at any site during case/outbreak investigations. Targets were set in terms of proportions of different premises and areas to be inspected, based on three classifications of priority areas.
- **Strengthening information system for effective disease surveillance and response Communicable Disease Control Information System (CDCIS)**
  Comprehensive national computerised CDCIS provides platform for systematic reporting of disease notification, disease registration, case investigations, case follow-up, and early warning system.
- **Legislative changes**
  The main legislative control, Destruction of Disease-Bearing Insects Act, 1975, was amended and new provisions for heavier penalties became enforceable from January 2001. This amendment aimed at big offenders such as housing developers and factory owners where the earlier penalty was not deterrent enough.
- **Community participation and intersectoral collaboration - national cleanliness and antimosquito campaigns**
  In 1999, the Government reaffirmed its commitment towards the control of mosquito-borne diseases such as dengue by the launching of a multi-ministerial National Cleanliness and Anti-Mosquito Campaign.
- **Changing insecticide fogging formulation and mass abating**
  Traditionally, malathion was the chemical of choice for dengue control in Malaysia. However, the acceptance of fogging inside houses was low as malathion has unpleasant smell and diesel-solvent left oily residues on the floors and walls of the houses. The use of malathion was stopped in 1996 and replaced with water-based pyrethroid fogging formulations such as Resigen and Aqua-resigen. In 1998, use of Abate larvicide on a large scale in high-risk areas was initiated to reduce Aedes larval density.

Despite decades of control programmes, mosquito population is still abundant and dengue incidence persists with outbreaks occuring in affected communities worldwide.[24] Besides, it was said that there was no evidence that vector-control efforts such as massive use of insecticides have significant effect on dengue transmission.[25]The recognition of the link between zika virus and microcephaly recently led to renewed global interest in *Aedes* control.[23] Thus, the need for evidence-based selection of the most appropriate, cost-effective and environmentally save interventions for *Aedes* control has never been greater. Hence, this health technology assessment was requested by the Head of Vector Borne Disease Sector, Disease Control Division, Ministry of Health.

2 TECHNICAL FEATURES

Integrated Vector Management (IVM) is an approach using both chemical and non-chemical methods, including environmental management.[26] It is part of a comprehensive strategy encompassing a variety of other vector control methods such as collaboration with the health sector and other sectors, educational campaigns, advocacy, social mobilisation, evidence based decision making and capacity building.[27] This strategic framework, adopted in 2004 for all vector-borne diseases is a rational decision making process for the optimal use of resources for vector control. The approach seeks to improve the efficacy, cost-effectiveness, ecological soundness and sustainability of disease-vector control. It is based on evidence and integrated management, promoting the use of a range of interventions selected on the basis of local knowledge about the vectors, diseases and disease determinants. The WHO issued a position statement on IVM in vector-borne disease control, and member states were invited to accelerate the preparation of national policies and strategies.[28]

The ultimate goal is to prevent the transmission of vector-borne diseases such as malaria, dengue, Japanese Encephalitis and Chagas disease. The Global Strategic Framework for IVM identifies five key elements for the successful implementation of IVM (Table 1). [22]

Table 1: Key elements of an integrated vector management strategy

Element	Description
Integrated approach	Integration of non-chemical and chemical vector control methods, and integration with other disease control measures
Evidence-based decision making	Adaptation of strategies and interventions to local ecology, epidemiology and resources, guided by operational research, entomological and epidemiological surveillance, subject to routine monitoring and evaluation
Advocacy, social mobilisation and legislation	Promotion and embedding of IVM principles in designing policies in all relevant agencies, organizations and civil society; establishment or strengthening of regulatory and legislative controls for public health; empowerment of communities
Collaboration within the health sector and with other sectors	Consideration of all options for collaboration within and between public and private sectors, application of principles of subsidiarity in planning and decision making, strengthening channels of communication among policy-makers, vector-borne disease programme managers and IVM partners
Capacity building	Provision of the essential material infrastructure, financial resources and human resources at national and local level to manage IVM strategies on the basis of a situational analysis

These elements should be supported by legislation and regulation. IVM is a step towards an integrated disease management approach that incorporates all components of disease control, including vector control, prevention, treatment and human vulnerability. [28]

In principal, control intervention can be categorised as chemical intervention (insecticide, chemical larviciding), habitat management, non-chemical larviciding (larvivorous fish, oil coating and mass trapping of larvae), population replacement methods and genetic techniques.[7] Organophosphates and pyrethroids are mainly used against Aedes spp. Insecticides can be used against adult mosquitoes and larvae in the forms of space treatment, indoor residual spraying, insecticide treated bed nets,barrier spraying, using attractive toxic baits and as larvicides.[29] Space spraying is carried out by backpack, truck-or air-craft mounted equipment. Barrier spraying of residual insecticides on external walls of houses and vegetation used to reduce exposure to exophilic mosquito. Residual insecticides are used on surface that adult mosquito frequently land on such as wall, ceiling, curians, vegetation, lethal ovitrap oviposition strips etc.[30] There is evidence that indoor residual spraying (IRS) is effective for controlling *Aedes aegypti* primarily due to its indoor resting behaviour. [31] Larviciding is predominantly with *Bacillus thuringiensis israelensis (Bti),* which is a gram positive, spore forming bacterium that is pathogenic to mosquitoes; and others such as spinosad, Insect Growth Regulator (methoprene, pyriproxyfen) and chitin synthesis inhibitors (Diflubenzuron, Novaluron). [30] Habitat (source) management attempts to reduce mosquito breeding sites by removing potential breeding sites. [32] Many countries enforce these measures by public education or by punitive methods through the legal system.[33] Environmental sanitation involves permanent elimination of containers producing *Aedes sp*. such as establishing reliable supplies of piped water, municipal reuse recycling programme (glass, metal, plastic), used-tire recycling operation and replacing septic tanks with sewerage. [30] Population control methods, such as the use of *Wolbachia spp* as well as genetic manipulation of mosquito population (introduction of sterile male) are emerging methods of vector control.[34] (Figure 1-3).

Effective vector based dengue prevention involves initiating control measure such as source reduction and larvicide treatment before the beginning of vector season, and adult reduction measure following detection of human arbovirus activity. Containment may be initiated whenever a suspected imported or locally acquired case is detected. During outbreaks, a combination of containment and large scale vector control may be used to minimise vector-human contact. [30]

The US Centre for Disease Control (CDC) highlighted that vector surveillance is a key component of any local IVM programme. Data derived from the vector surveillance primarily estimates mosquito abundance, and this estimate is used to indicate level of risk. The indicators that are commonly used can be broadly divided into i) immature stage (larvae and pupae) survey indices, ii) eggs per ovitrap per week, iii) female mosquitoes per sticky gravid trap per week, and iv) adult infection rates. [30]

Larval surveys usually involve identifying all immature mosquitoes in every container in the target area, home, community etc. The container indices below are computed:-[35]

- House Index : percentage of houses with at least one positive container
- Container Index : percentage of all containers with water that are larva/pupae positive
- Breteau Index : number of positive containers per 100 houses

Mosquito threshold for dengue, chikungunya and zika virus transmission using larval indices should be determined by each local vector control programme. The following container *Aedes* threshold values for dengue transmission has been reported, BI=1.2,CI=1.8% and HI=1%.[36]

Pupal surveys (pupae per house, per person or per hectare) are based on the assumption that pupal productivity is a better estimate of the adult population than the traditional indices (HI,CI, BI) or larval counts. Pupal surveys to determine dengue, chikungunya and zika virus transmission should be determined by local vector control programme. Some models showed that it takes between 0.5 and 1.5 *Ae aegypti* pupae per person to sustain dengue transmission at 28^{0}C in a human population with 0-67% immunity. [37]

For eggs per ovitrap per week, absence of severe dengue cases was noted when the density of *Ae aegypti* eggs per ovitrap per week was less than two.[38] Ovitraps are device used to detect the presence of *Aedes sp* when the population density is low and larval survey are largely unproductive (BI less than five) as well as normal condition. For adult infection rates, the infection indices are Minimum Infection Rate (MIR), Maximum Likelihood Estimates of the Infection Rate (MLE) and Vector Index (VI). However, adult infection rates cannot be used to predict outbreaks in dengue, chikungunya and zika virus surveillance programme because of limited data on infection rates and prevalence of human infection. [30]

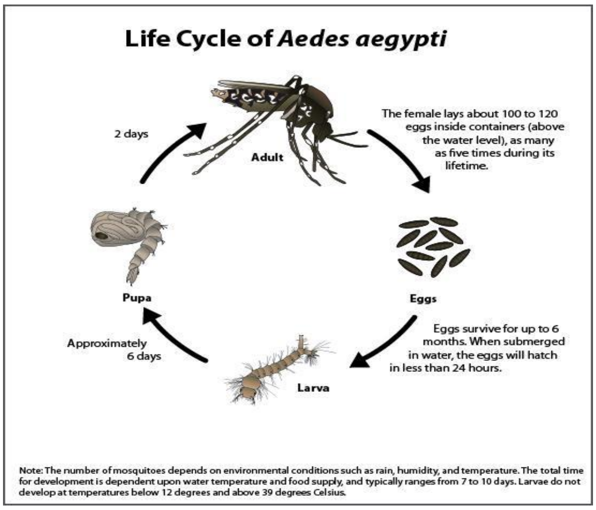

Figure 1: The life cycle of *Aedes Aegypti* (left) and female *Aedes aegypti* in the process of acquiring blood meal from her human host (right)

Figure 2: Adulticiding in *Aedes* control, (left) and larviciding using *Bacillus thuringiensis israelensis (Bti)* (right)

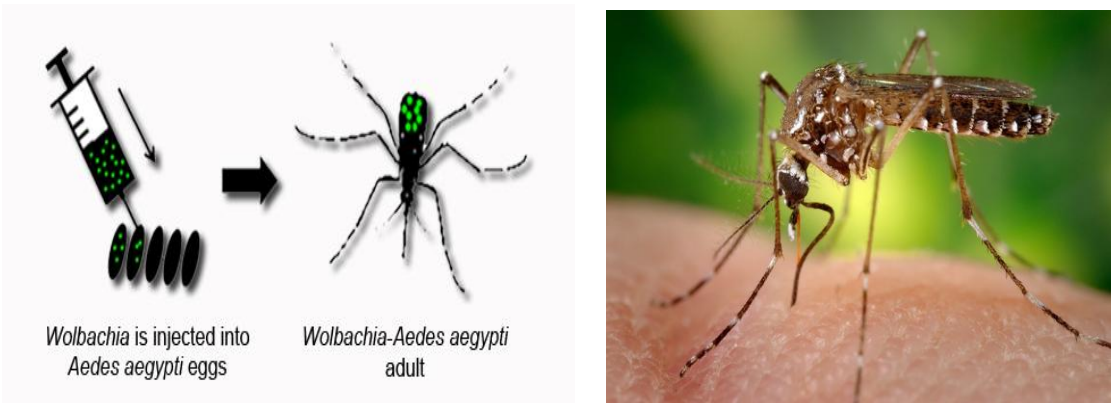

Figure 3: Emerging methods for vector control, population control method using *Wolbachia* (left) and genetically modified mosquito (right)

3 POLICY QUESTION

Which IVM strategies will be the most effective, safe and cost-effective approach for *Aedes* control in Malaysia?

4 OBJECTIVES

i. To determine the effectiveness of IVM for *Aedes* control compared with other control measures or no comparator
ii. To determine the safety of IVM for *Aede*s control compared with other control measures or no comparator
iii. To determine the economic, social, organizational, ethical and legal implications of IVM for *Aedes* control

4.1 Research questions

i. What is the effectiveness of IVM for *Aedes* control compared with other control measures or no comparator?
ii. How safe is IVM for *Aedes* control compared with other control measures or no comparator?
iii. What are the economic, organizational, social, ethical and legal implications of IVM for *Aedes* control?

5 METHODS

5.1 Literature search strategy

Studies were identified by searching electronic databases. The following databases were searched through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present. EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2019), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2019), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2019), EBM Reviews-Health Technology Assessment (1st Quarter 2019), EBM Reviews-NHS Economic Evaluation Database (1st Quarter 2019). Parallel searches were run in PubMed. Appendix 3 showed the detailed search strategies. No limits were applied to the search. The last search was run on 30 March 2019. Additional articles were identified from reviewing the references of retrieved articles. One of the tools used to assess the risk of bias and methodological quality of all the articles retrieved is the Critical Appraisal Skills Programme (CASP) checklist. All full text articles were then graded based on guidelines from the U.S./Canadian Preventive Services Task Force.

5.2. Study Selection

Based on the policy question the following inclusion and exclusion criteria were used:-

5.2.1 Inclusion criteria

Population Problems	*Aedes aegypti, Aedes albopictus, Aedes sp.*, mosquito, vector
Intervention	• Integrated vector management, combined vector control/strategies (two or more out of five IVM elements) • Existing control (IVM) and additional control method
Comparators	• Chemical control (indoor and outdoor spraying/fogging, residual spray with insecticides, container treatment with larvicides and lethal ovitraps/autodissemination trap; chemical insecticides belongs to pyrethroids,

	organophospates, organochlorine, carbamates,insect growth regulators) • Biological control [(larvivorous fish, insect predators, crustaceans (copepods), bacteria based *Bacillus thuringiensisvar israelensis, Bti*], • Physical/mechanical control (regular cleaning of containers, container covers and ovitraps) • Environmental management • Community mobilisation • Health education • Punitive methods via the legal systems • Mosquito population control methods [(use of *Wolbachia spp*., genetic manipulation of mosquito (e.g.introduction of sterile males)] • Adult trapping (BG trap, sticky trap, light trap, CO_2 trap) • Collaboration • Existing control (IVM) • No comparator
Outcomes	i. Effectiveness of IVM for *Aedes* control • Entomological infestation indices/parameters: o Breteau Index (BI): Number of positive containers with *Aedes sp* larvae per 100 houses o Household Index (HI)/Aedes Index (AI): Percentage of houses positive with immature (larvae/pupae or both) o Container Index (CI): percentage of containers specifically designed for water storage positive for immature (larvae/pupae) o Mosquito density (number of adult mosquitoes per number of houses surveyed) o Ovitrap positivity rate (number of mosquito traps with eggs, divided by total number of traps multiplied by 100) o Pupae index (number of pupae per 100 houses inspected) • Incidence/cases of Dengue/vector-borne disease caused by *Aedes sp* • Mortality from Dengue/vector-borne disease caused by *Aedes sp* • Larva density (mean number of larva per container) • Mosquito mortality rate • Pupae per person index (number of pupae collected per human population in a sector) ii. Safety of using IVM for *Aedes* control • Any reported adverse outcome or unintended

	consequences on people or the environment iii. Cost analysis, cost-effectiveness, cost-utility of IVM for *Aedes* control iv. Economic, social, organizational, ethical and legal implications of IVM for *Aedes* control

- Study design: No restriction of study type. HTA reports, systematic review with/without meta-analysis, randomised controlled trial (RCT), non-randomised trial, observational studies (cohort, case-control, cross-sectional) and economic evaluation studies

- Full text articles published in English.

5.2.2 Exclusion criteria:-

- Study design: Animal study, laboratory study, narrative review, case reports.

- Non English full text article.

Based on the above inclusion and exclusion criteria, study selection were carried out independently by two reviewers. All identified citations (titles and abstracts) were assessed for the above eligibility criteria. If it was absolutely clear from the title and / or abstract that the study was not relevant, it was excluded. If it was unclear from the title and / or the abstract, the full text article was retrieved. Two reviewers assessed the content of the full text articles and did the data extraction. Disagreements were resolved by discussion. The report protocol is shown as in Appendix 2.

5.3 Critical appraisal of literature

One of the tools used to assess the risk of bias and methodological quality of all the articles retrieved is the Critical Appraisal Skills Programme (CASP) checklist. The CASP checklist is as in Appendix 4. It consists of eight critical appraisal tools designed for these study designs; SR, RCT, cohort studies, case control studies, economic evaluations, diagnostic studies, qualitative studies, and clinical prediction rule. Assessment of the risk of bias was done by two reviewers and achieved by answering a pre-specified question of criterias assessed and assigning a judgement relating to the risk of bias as either:

+	Indicates YES (low risk of bias)
?	indicates UNKNOWN risk of bias
-	Indicates NO (high risk of bias)

All full text articles were then graded based on guidelines from the U.S./Canadian Preventive Services Task Force (Appendix 1).

5.4 Analysis and synthesis of evidence

5.4.1 Data extraction strategy

Data were extracted from the included studies by a reviewer using a pre-designed data extraction form (evidence table as shown in Appendix 5) and checked by another reviewer. Disagreements were resolved by discussion. Details on: (1) methods including study design, (2) study population (3) type of intervention, (4) comparators, (5) outcome measures including economic evaluation and organizational issues were extracted. Other information on author, journal and publication year, and study objectives were also extracted. The extracted data were presented and discussed with the expert committee.

5.4.2 Methods of data synthesis

Data on the effectiveness, safety, cost-effectiveness, economic, social, organizational, ethical and legal implication of IVM for *Aedes* control were presented in tabulated format with narrative summaries. No meta-analysis was conducted for this review.

6 RESULTS

A total of 702 titles were identified through the Ovid interface: MEDLINE(R) In-process and other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present, EBM Reviews-Cochrane Database of Systematic Reviews (2005 to March 2019), EBM Reviews-Cochrane Central Register of Controlled Trials (March 2019), EBM Reviews-Database of Abstracts of Review of Effects (1^{st} Quarter 2019), EBM Reviews-Health Technology Assessment (1^{st} Quarter 2019), EBM Reviews-NHS Economic Evaluation Database (1^{st} Quarter 2019), Embase 1996 to 2019 week 10 and PubMed. Twenty-eight were identified from references of retrieved articles. After removal of 72 duplicates, 658 titles were screened. A total of 658 titles were found to be potentially relevant and abstracts were screened using the inclusion and exclusion criteria. Of these, 553 abstracts were found to be irrelevant. One hundred and five potentially relevant abstracts were retrieved in full text.

After applying the inclusion and exclusion criteria and critical appraisal to the 105 full text articles, 19 full text articles were included and 88 full text articles were excluded. (Figure 4). Twelve (12) out of the 19 included articles were related to effectiveness of IVM for *Aedes* control whereas the other five were related to cost-effectiveness and two on the social implications of IVM for *Aedes* control. The 19 full text articles finally selected for this review comprised of five systematic review with/without meta analysis, three cluster

RCTs, one cohort study, four pre-post intervention studies, one cross sectional study, three cost-effectiveness analysis and two cost analysis.

Eighty-eight articles were excluded as those primary studies were already included in the systematic review (n=19), irrelevant study design (n=21), irrelevant population (n=2), irrelevant intervention (n=40), and irrelevant outcome (n=6). The excluded articles were listed as in Appendix 6. There was no Health Technology Assessment (HTA) report retrieved on IVM for Aedes control, however several guidelines were available.

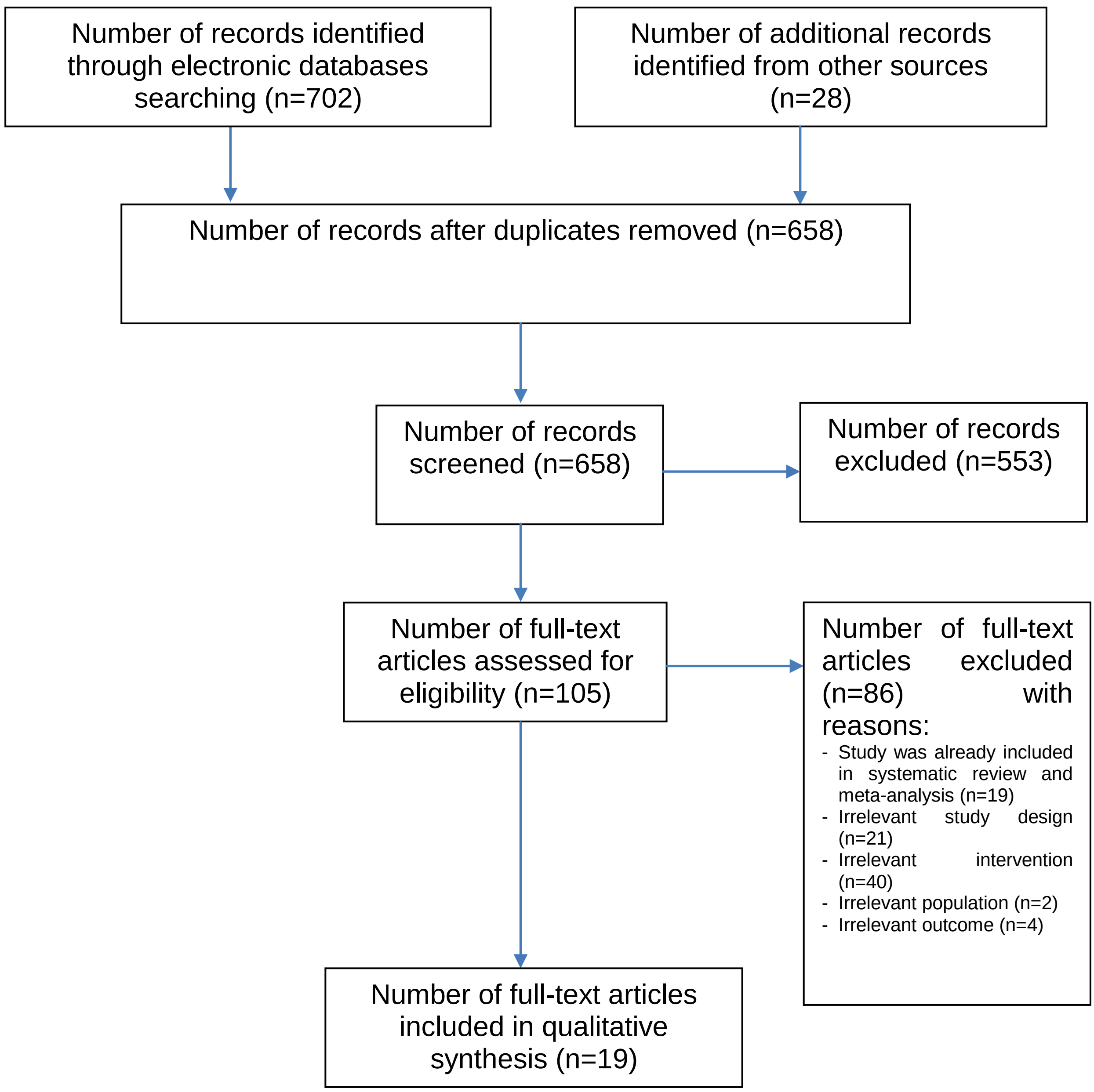

Figure 4: Flow chart of study selection

6.1 STUDY DESCRIPTION

Of the 19 included articles, twelve studies were included in the effectiveness section in this review. The other five studies were related to cost-effectiveness of IVM for *Aedes* control and two on social aspect of IVM for *Aedes* control.

The included articles were published between 2006 and 2017. Most of the studies were conducted in Brazil and Thailand, followed by Mexico, Cuba and UK (two studies), and one study each from Argentina, Canada, Australia, Malaysia and Switzerland. This review included altogether a total of 814,149 residents from all the studies, involving 194,797 households. Sample size for each of the included studies ranged from 1800 to 470,000 subjects. The longest follow-up of the included study was up to ten years. Most of the study participants were residents in urban and peri urban dengue transmission areas as well as students.

6.1.1 Risk of bias

Risk of bias assessment in the included studies are summarised according to their study design as below.

Criteria assessed	Authors look for the right type of papers?	Selection of studies (all relevant studies included?)	Assessment of quality of included studies?	If the results of the review have been combined, is it reasonable to do so (heterogeneity)?
Bowman et al.2016 [39]	+	+	+	+
Erlanger et al.2008 [20]	+	+	?	+
Castro et al. 2017 [40]	+	+	+	+
Muhandis et al. 2011 [41]	+	+	?	+
Lima et al. 2015 [4]	+	+	?	+

Figure 5a: Assessment of risk of bias of systematic review (CASP)

Criteria assessed	Adequate sequence generation	Allocation concealment	Blinding of participants and personnel	Incomplete outcome data addressed	Free of selective reporting	Free of other bias
Caprara et al.2015 [45]	+	?	?	+	+	?
Foster et al.2015 [46]	+	?	?	+	+	?
Kittayapong et al.2012 [47]	+	?	?	+	+	?

Figure 5b: Assessment of risk of bias of RCT (Cochrane)

Criteria assessed	Selection of cohort	Exposure accurately measured	Outcome accurately measured	Confounding factors	Follow-up of subjects
Gurtler et al.2009 [41]	+	+	+	?	+

Figure 5c: Assessment of risk of bias of cohort (CASP)

Criteria assessed	Kittayapong et al.2008	Kittayapong et al.2006
Question or objective clearly stated?	+	+
Eligibility/selection criteria for study population clearly described?	+	+
Were participants representative for those who would be eligible for the test/ service/intervention in the population of interest?	+	+

Criteria assessed	Kittayapong et al.2008	Kittayapong et al.2006
Were all eligible participants that met the prespecified entry criteria enrolled?	+	+
Sample size sufficiently large to provide confidence in findings?	?	?
Test/service/intervention clearly described and delivered consistently?	+	+
Outcome measures prespecified, valid, reliable, and assessed consistently?	+	+
People assessing the outcome measures blinded to participants exposure/ interventions?	?	?
Loss to follow-up after baseline 20% or less? Loss to follow-up accounted for in the analysis?	?	?
Statistical methods examine changes in outcome measures from before to after intervention? p value?	+	+
Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?	+	+
If intervention conducted at group level, did statistical analysis take into account of individual level data to determine effects at group level?	+	?

Figure 5d: Assessment of risk of bias of pre-post intervention (CASP)

Criteria assessed	Mendoza-Cano O et al. 2017	Luz PM et al. 2011	Baly A et al. 2007
A well-define question posed?	+	+	+
Comprehensive description of competing alternative given?	+	?	+
Effectiveness established?	+	+	+
Effects of intervention identified, measured and valued appropriately?	+	+	+
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	+	+	+

Costs and consequences adjusted for different times at which they occurred (discounting)?	+	?	?
Results of the evaluation?	+	+	+
Incremental analysis of the consequences and costs of alternatives performed?	?	+	+
Sensitivity analysis performed?	?	+	?

Figure 5e: Assessment of risk of bias of economic evaluation (CASP)

6.2 EFFECTIVENESS

Twelve studies reported on effectiveness of IVM for *Aedes* control, of which five are SR with/without meta analysis, three cluster RCTs, one cohort study, two pre-post intervention studies and one cross sectional study.

- **DENGUE INCIDENCE**

Bowman et al. (2016) conducted a systematic review and meta analysis aiming to to review randomised and non-randomised studies to evaluate effectiveness of vector control intervention in reducing Aedes sp indices and human DENV infection/disease. They included studies of any design published since 1980 if they evaluated control methods (singly or combined) targeting *Ae aegypti* or *Ae albopictus* for at least three months (minimum period required to demonstrate a sustained impact on vector population/dengue transmission). Outcome of this review were dengue incidence and/or entomological indices [Breteau Index(BI), House Index (HI), Container Index (CI), tank positivity, number of mosquito adults, pupae per person index (PPI), presence of Aedes immature and ovitrap positivity rates]. Systematic search was conducted from these databases; WHOLIS, MEDLINE, EMBASE, LILACS, with last search conducted on the 10th January 2015. PRISMA group guideline was followed as standard methodology. Tools used for risk of bias assessment were Cochrane risk of bias tool (RCT), while for non-RCT, Quality Assessment Tool for quantitative study (Thomas BH et al. 2004) was used. Intervention assessed was combined intervention or single intervention for Aedes aegypti/albopictus control used for more than three months. Frequently evaluated interventions were clean up programme, outdoor fogging, education, larviciding and water jar covers. The review finally included 41 studies, nine RCTs comprising of two RCTs and seven cluster randomised controlled trial (cRCT), and 32 non randomised studies (consisting of various designs; seven longitudinal studies, four interrupted time series, eight controlled trials, five before and after studies, six observational studies and two models). The included studies were from South East Asia (11), South Asia (8), Australasia (4), South America (5), Central America (10), North America (3).

Pooled results for dengue incidence outcome were available for interventions from several non-randomised trials.(Figure 6) In terms of dengue incidence, the result showed that combined community based environmental management together with the use of water container cover reduced the odds to 0.22(95%CI

0.15,0.32;p<0.0001)(one study). The presence of house screening in homes significantly reduced the odds of dengue incidence compared to homes without screens (OR=0.22, 95%CI 0.05, 0.93; p=0.04) (three studies). In contrast, the use of knockdown sprays (one study) or mosquito coils (two studies) was significantly associated with increased odds of dengue incidence (OR=2.03, 95%CI 1.44, 2.86) and (0R=1.44; 95%CI 1.09,1.91) respectively. Heterogeneity across the studies was high, most probably due to varying study designs, number of study population and interventions, with I^2 of 92.1%. The other interventions, indoor residual spraying, the use of mosquito repellents, bed nets or mosquito traps did not significantly associated with the odds of dengue infection. [39 level II-1]

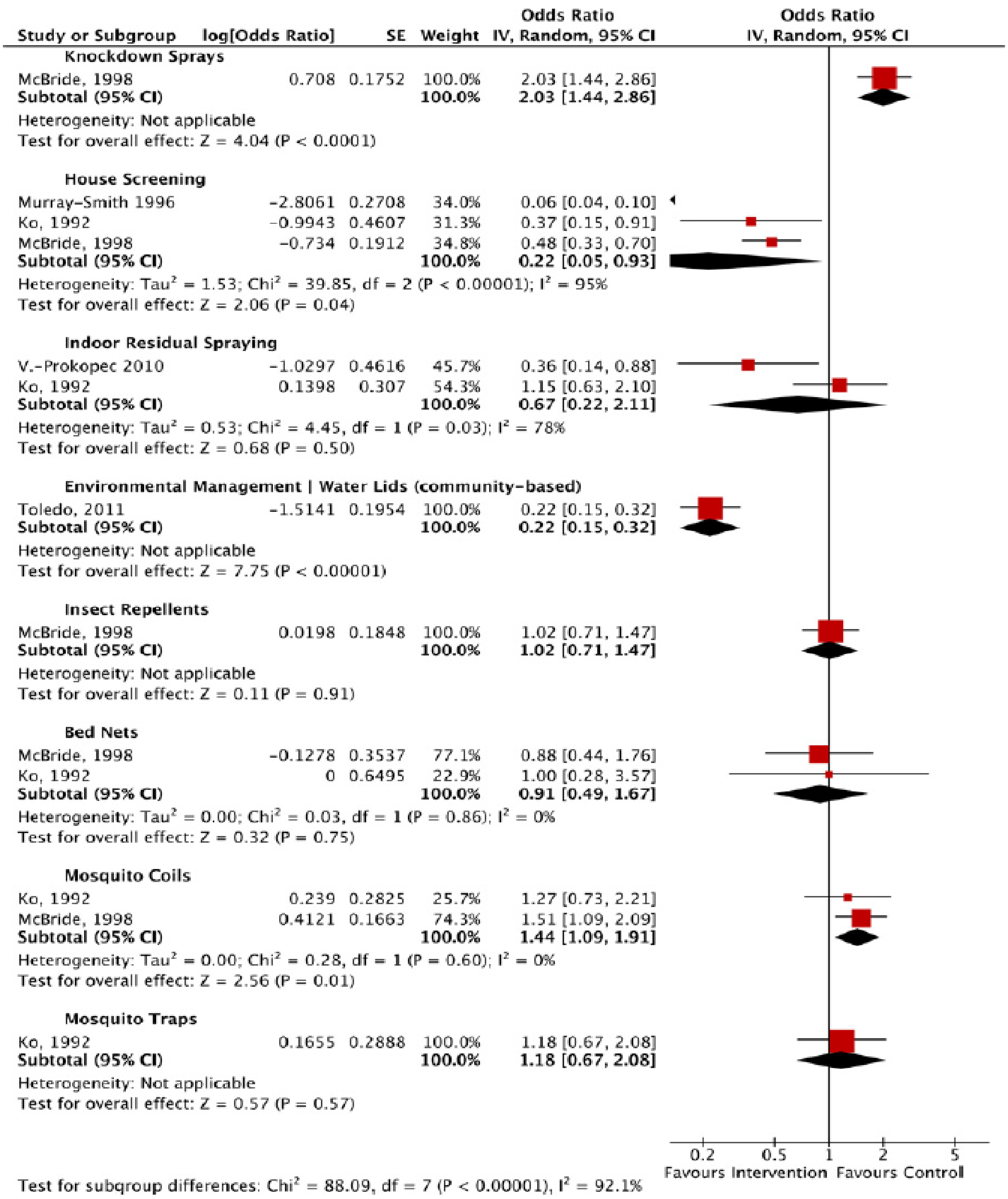

Figure 6: Forest plot of OR for dengue incidence, stratified by intervention in non-randomised controlled trial

Another quasi RCT was conducted by Ocampo et al. (2014) to test vector control strategy in Palmira and Buga towns, Colombia. The study targeted 4800 catch basins in the entire urban area of Buga, southwestern Columbia. Potential breeding sites inside and outside houses were first characterized, and personnel trained assessed their productivity based on pupae/person index. Simultaneously, training and monitoring were implemented to improve dengue case surveillance system. Entomological data was used to define the targeted intervention. Quasi experimental design used to assess the efficacy of intervention in positivity index of targeted and non-targeted breeding sites and impact on dengue cases.They found street catch basin (storm drains) were the potential breeding site most frequently found containing *Aedes* immature stages in the baseline. A significant decrease in catch basin positivity for *Aedes* larvae was observed after each monthly treatment (p<0.001). They also found larviciding using the insect growth regulator Pyriproxyfen delivered as part of a community-based strategy significantly reduced the rate of dengue incidence in the intervention group (RR=0.19,95%CI 0.12,0.30), p<0.0001, a five-fold reduction in 18 months study. [40 level II-1]

Gurtler et al. (2009) conducted a cohort study to describe the implemented intervention programme and assess long term effect of vector suppressive action on *Aedes aegypti* indices and incidence of dengue during the 5-year period. The study was based on a before-and-after citywide assessment of *Aedes aegypti* larval indices and the reported incidence of dengue in Clorinda, northeastern Argentina over 2003-2007. Intervention was focal treatment with larvicides of every mosquito developmental site every four months (14 cycles), combined with source reduction and ultra-low-volume insecticide (ULV) spraying during emergency operation (combination of chemical, physical control and education). The desired control program target was House Index (HI)<1% and Breteau Index (BI)<5. Preliminary survey was done to establish infestation level. The team also did container inspection, emptied disposable containers, larviciding with 1% temephos in sand granules at 1mg per litre or with *Bacillus thuringiensis israelensis* BTi,VectobacR), of 1,808 random occupied houses (baseline houses visited in 2002). A total of 14 cycles of focal treatment were conducted at four-months interval (from 2003 to 2007). Concurrently, educational efforts were conducted in schools. Evaluation survey was done among those conducting regular control, assessing impact of larviciding shortly after in a convenience sample of blocks. Finally the total houses visited were 168,603, and 120,967 have been inspected in five years (2003-2007).

They found incidence of dengue cases declined from 10.4 per 10,000 in 2000 (by DEN-1, 46 confirmed cases and 500 suspect cases) to 0 from 2001 to 2006, then rose to 4.5 cases per 10,000 in 2007(by DEN-3) (Figure 7). [41 level II-2]

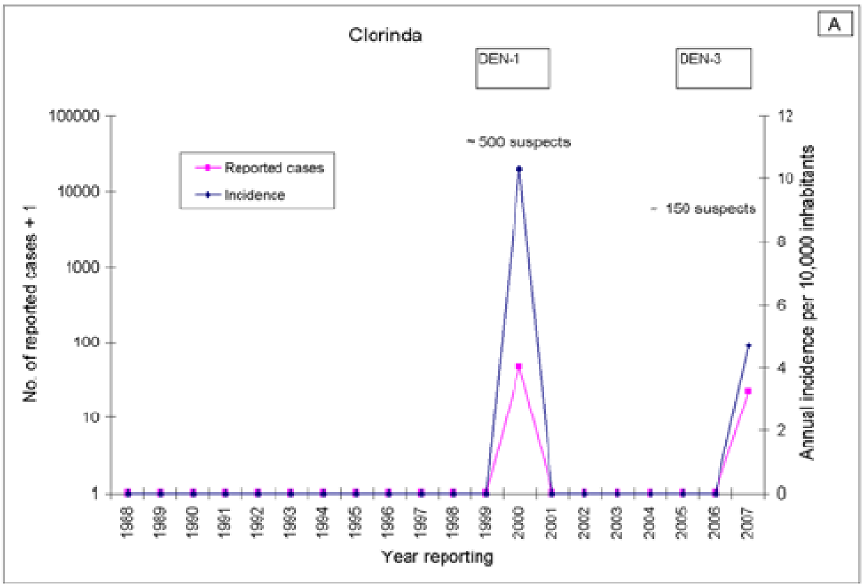

Figure 7: Reported cases and incidence of dengue in Clorinda, Argentina, 1988-2007 (Gurtler et al. 2009)

Kittayapong et al. (2006) in a pre and post intervention study aimed to report a cost-effective successful vector control intervention with emphasis on the integrated biological and physical control methodologies and the community participation approach. The study was conducted at transmission foci in Plaeng Yao District (rural and semi rural village), Chachoengsao Province, eastern Thailand. Intervention was carried out in Hua Sam Rong subdistrict, whereas control village was in the Wang Yen subdistrict.

Implementation was done by the local community in collaboration with local administration, public health, and school authorities. In this study, the intervention were; source reduction campaign with appropriate vector control technologies (screen covers for water jars, a combination of *Bacillus thuringiensis subsp. israelensis* and *Mesocyclops thermocyclopoides* for various permanent containers other than water jar, and Permethrin-treated lethal ovitraps) applied within the foci (within 100 m around the foci) and also within schools attended by children from the treated areas. Intervention was targeted to dengue foci, defined as group of houses within 100m radius of case houses that had IgM and IgG positive students. Areas outside dengue foci were group of houses that had no IgM and IgG positive students (controls). Larval surveys were conducted before and after vector control activities commenced. Larval positive houses and the number of larvae sampled were recorded and integrated into the GIS map. The post intervention follow up was up to 71 weeks.

Baseline larval survey showed that the larval abundance were between 0 and 889 per house (Intervention village) and between 0 and 1418 (control village), with average number of larvae per house of 234.56±27.32 and 132.57±17.41, for intervention and control village respectively.

They found **reduction in dengue** hemorrhagic fever (DHF) case rates, with 265.25 versus 217.86 per 100,000 population, in the treated and untreated villages respectively, in the year before intervention compared with 0 versus 322.23 per 100,000 population, respectively, in the year after intervention.

They concluded that significant reduction of dengue vectors and dengue hemorrhagic fever cases in treated areas compared with untreated areas have been demonstrated. However, the long-term success of the program and the level of involvement of the communities need to be evaluated over time. [42 level II-3]

Kittayapong et al. (2008) conducted another pre-and post intervention study to report a strategy for integrated, community-based dengue control intervention suitable for semi-rural and rural Thailand that could successfully affect dengue transmission in a targeted community. A serological survey of primary school children from six schools in Chachoengsao Province, Thailand, (approximately 1800 students, ranging from kindergarten to grade 12) was performed at the end of the peak of dengue transmission. Geographic Information System (GIS) analysis of sero-positive cases was carried out to determine transmission foci for targeting control implementation. Vector control implementation was conducted in the foci and within 100 meters around the foci. The areas of dengue foci were defined as group of houses within 100m radius of the house that had IgG and IgM positive students. The areas outside of dengue foci were defined as houses within 100m radius of the houses that had no IgG and IgM positive students.

Intervention was integrated community based intervention which consisted of; source reduction (clean-up campaign followed by weekly garbage pick-up) together with the use of screen covers for water jars, a combination of *Bacillus thuringiensis subsp. israelensis* and *Mesocyclops thermocyclopo*ides (for other water container apart from jars), and Permethrin-treated lethal ovitraps. Untreated areas in Wang Yen Subdistrict were regarded as control. Implementation of vector control strategies in the foci was continued until the end of the rainy season. Vector control effectiveness was monitored using entomological, serological, and clinical parameters up to two years. Sera were tested for IgM and IgG. Enzyme-linked immunosorbent assay (ELISA) test for serology was carried out according to the MAC-ELISA test routinely used at the Mahidol University.

They found the **significant reduction in sero-positive children** (the proportion of IgG-IgM positive students in the treated areas reduced from 13.46% (first year) to 0% (second year), whereas those from untreated areas increased. (Table 2)

Table 2: Comparison of serologically positive children and clinical cases of dengue in treated and untreated areas before and after vector control intervention

Group	Serological %IgG-IgM+ve (n)		Clinical No. positive cases/100,000 population	
	Yr1 treated	**Yr2 Untreated**	**Yr1 treated**	**Yr2 Untreated**
Treated area	**13.5(83)**	**0.0(98)**	265.3	0.0
Untreated area	**9.4(66)**	**19.2(69)**	217.9	322.2

Significant **reduction of clinical cases** in the treated areas compared to untreated was also reported. (Table 2)

The authors concluded integrated vector control tools (source reduction, the use of screen covers, a combination of *Bacillus thuringiensis subsp. israelensis* and *Mesocyclops thermocyclopoides* and Permethrin-treated lethal ovitraps) together with community participation could suppress dengue transmission. 43 level II-2

The effectiveness of various interventions on incidence of dengue are summarised in the Table 3 below.

Table 3: Summary effectiveness of various controls on incidence of dengue

Study	Intervention	Population	Effect measure	Length of study
Bowman et al. (2016) *SR with MA - non randomised trial*	Combined community based environmental control and water container cover	Toledo 2011	0R=0.22 (95%CI 0.15,0.32)	-
	House screening	MurraySmith 1996 Ko 1992 McBride 1998	pool 0R=0.22 (95%CI 0.05,0.93)	-
	Knock-down spraying	McBride 1998	0R=2.03 (95%CI 1.44,2.86)	-
	Mosquito coils	Ko 1992	0R=1.44 (95%CI 1.09,1.91)	-
Ocampo et al.(2014) *QuasiRCT (Colombia)*	Larviciding using insect growth regulator (pyriproxyfen) & community based strategy	4800 catch basins	RR=0.19 (95%CI 0.12,0.30)	18 months
Gutler et al.(2009) *Cohort (Argentina)*	Focal treatment with larvicide (temephos/Bti) every 4 months (14 cycles), source reduction, ULV spraying & school education	Total houses visited =168,603 Total houses inspected = 120,967 (2003-2007)	**Incidence of dengue** (per 10,000 population) • 10.4/10,000(2000)* • 0/10,000(2001-2006)* • 4.5/10,000(2007) ** *DEN-1 **DEN-3	5 years
Kittayapong et al. (2008) *Pre-post intervention (Thailand)*	Integrated community based intervention; source reduction, screen cover for water jar, *Bti/mesocyclopes* for other container, permethrin treated lethal ovitrap; in the foci and within 100m around the foci	n=1800 primary school children from six schools in Chachoengsao Province, Thailand, (ranging from kindergarten to grade 12)	**No. of DHF case** (per 100,00 population) • 265.3 to 0/100,000 (treated) • 217.9 to 322.2/100,000 (untreated) **Serology** (Percent IgG-IgM positive) • 13.5 to 0 (treated) • 9.4 to 19.2 (untreated)	1 year

- **VECTOR/ENTOMOLOGICAL INDICES**
- **Breteau Index (BI)**

In the systematic review by Bowman et al. (2016), article with these interventions; insecticide treated curtains, community based combination intervention such as waste disposal, clean up campaigns, formation of community working groups, mobilisation and education; source reduction, larviciding, entomological surveillance, communication, education and punitive fines, were available for analysis for outcome on vector indices [Breteau Index (BI), House index (HI), Container Index (CI) and pupal indices].

Bowman et al. (2016) reported that community based combined intervention significantly reduced BI with rate ratio ranging from 0.48(95%CI 0.26, 0.89) to 0.65(95%CI 0.52, 0.81) and mean difference of -4.66(95%CI -5.89,-3.43). (Table 4).

Table 4: Effectiveness of community based combined intervention for BI (in SR by Bowman et al. 2016)

References	Design	Intervention	Effect measure (rate ratio/mean difference/odds ratio)(95%CI)
Vanlerberghe et al. 2010	cluster randomised trial	Community based environmental modification, larvicide, water cover, social mobilization	**0.48* (0.26,0.89)**
Castro et al. 2012	cluster randomised trial	Community based clean up, social mobilisation, education, inspection	0.65***** (0.52,0.81)
Arunachalam et al. 2012	cluster randomised trial	Community based environmental management, water covers, social mobilisation, clean up	**-4.66# (-5.89,-3.43)**
Gurtler et al. 2009	pre and post intervention study	Larvicide, source reduction, ULV fogging, house inspection	0.15^ (0.10, 0.24)

* rate ratio # mean difference ^odds ratio

However, insecticide treated curtains did not significantly reduced the pooled mean difference for BI, (two studies), compared to control (MD= -25.16; 95%CI -76.02,-25.70).(Figure 8). [39 level II-1]

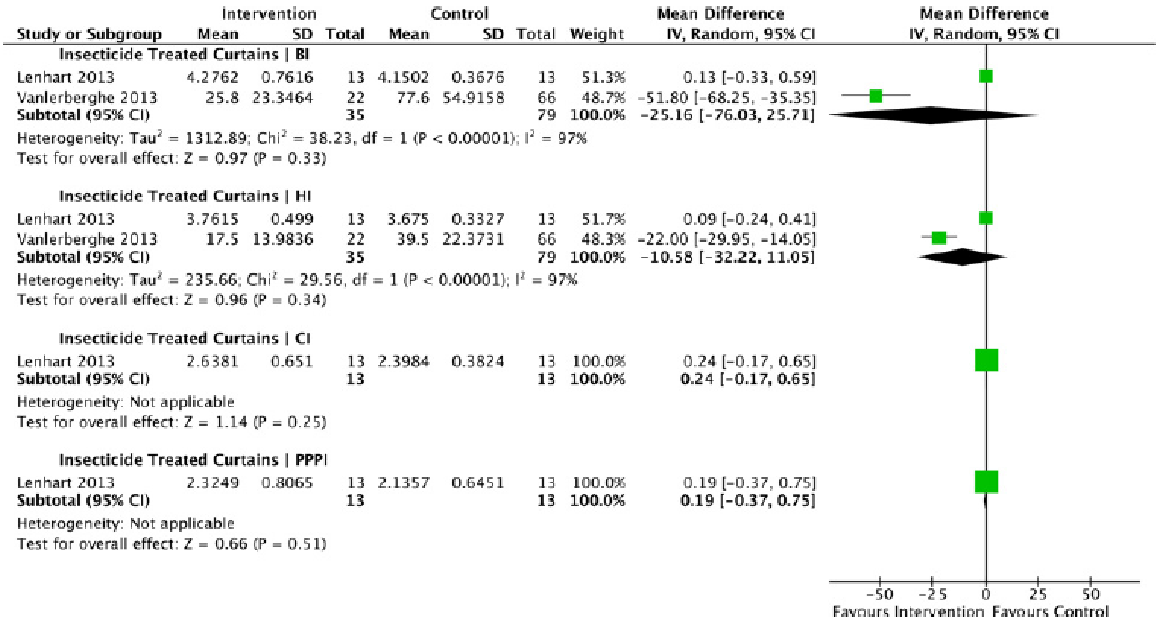

Figure 8: Forest plot of mean difference between insecticide-treated curtains intervention and control for Breteau Index, House Index, Container Index and PPPI in cluster randomised controlled trial

Erlanger et al. (2008) conducted a systematic review and meta analysis to compare the effects of different dengue control interventions (ie biological control, chemical control, environmental management and integrated vector management) with respect to the following entomological parameters (BI, CI, and HI). Systematic search was done from these databases; PubMed, ISI web of Science, Science Direct, Dengue Bulletin of the WHO up to December 2007. The review assessed different dengue control interventions (ie. biological control, chemical control, environmental management (EM) and integrated vector management in developing countries. Environmental Management assessed was comprised of these components i) environmental modification ii) environmental manipulation iii) modification or manipulation of human habitation of behavior to reduce human-vector contact. Studies from less and medium developed countries (Human Development Index ≤0.8, UNDP 2008), with four exceptions: Cuba, Mexico, Trinidad & Tobago were included, and only studies with data could be transformed into BI, CI, HI or dengue incidence included. Outcome was measured **as relative effectiveness (RE)**, which is defined as proportion of vector population reduction in relation to pre-intervention level or control area without intervention; 1.0 minus relative reduction of measure such as BI. The RE equals to zero indicates elimination of vector population or dengue incidence, and relative effectiveness >1.0 indicates an increase in corresponding measure in the targeted area. In contrast, RE <1.0 indicates a reduction caused by the intervention, compared to control or pre-intervention phase. A total of 56 studies were finally included with varying study designs (RCT, cluster RCT, non randomised controlled trial, interrupted time series, pre-post intervention study, observational study) from 23 countries. They found these interventions according to the type of control; chemical control (19), biological control (10), environmental management (EM) (14), Integrated Vector Management (IVM) which further consisted of EM plus chemical

(8) and EM plus biological (10). Length of studies included ranged from 2.5 months to 20.5 months.

In the review, Erlanger et al. described the used chemical controls were temephos (Abate)(7), malathion (4), fanitrothion(4), pyrethoids (3) with these function; larviciding, adulticiding (indoor and outdoor),and the latter combination. Meta analysis was done only for studies that used outdoor adulticides measuring BI; (five studies). The pooled relative effectiveness (RE) for chemical control (outdoor adulticiding) against dengue vector measured by Breteau Index was 0.24(95%CI 0.05, 1.19). (Figure 9). [20 level II-1]

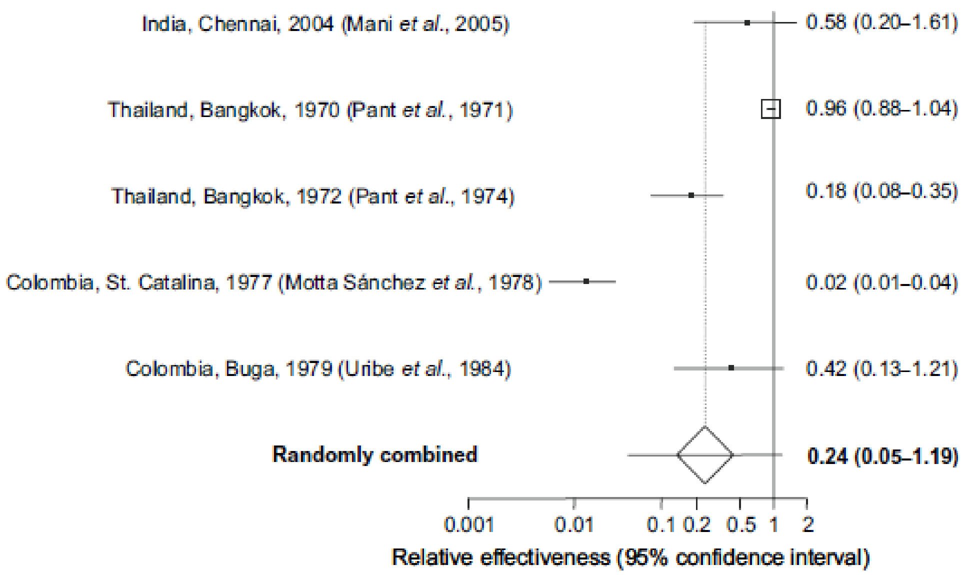

Figure 9: Performance (Relative Effectiveness) of chemical control (outdoor adulticiding) against dengue vectors measured by Breteau Index

In the smilar review, Erlanger et al. (2008) found for environmental management, the pooled RE was 0.71(95%CI 0.55,0.90) measured by BI (from 9 studies). Environmental Management assessed in the review encompassed these components i) environmental modification ii) environmental manipulation iii) modification or manipulation of human habitation of behavior to reduce human-vector contact (Figure 10).

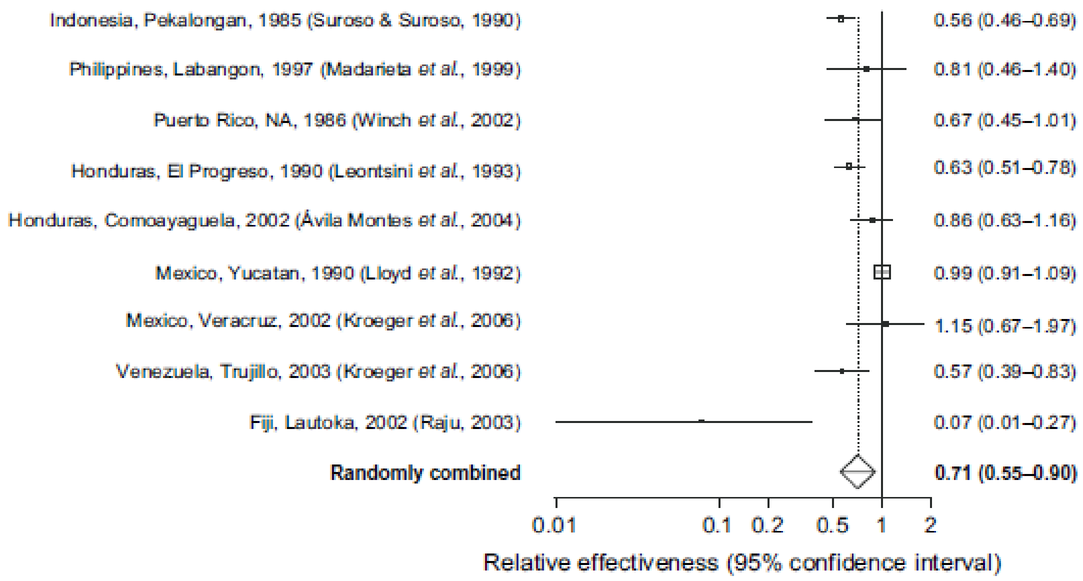

Figure 10: Performance (Relative Effectiveness) of environmental management against dengue vectors measured by Breteau Index

Meanwhile, in the review, the assessed IVM consisted of Environmental Management (EM) combined with chemical intervention (13), or EM combined with biological control (5). Pooled results for vector indices outcome (BI, HI and CI) were available from several studies (11,9, and 8) respectively.

They found that IVM (combination of EM and chemical control) was the most effective method to reduce the CI,HI, BI, with the following results. The pooled RE was 0.33 (95%CI 0.30,0.79) measured by BI for IVM (combination of EM and chemical control), (from 11 studies) (Figure 11). [20 level II-1]

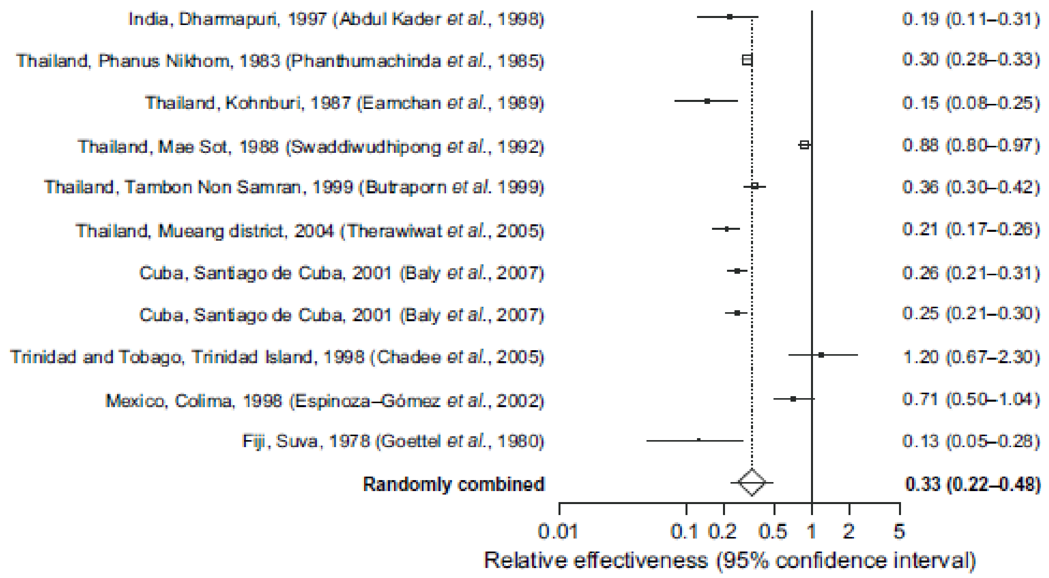

Figure 11: Performance (Relative Effectiveness) of IVM (combination of EM and chemical control) management against dengue vectors measured by Breteau Index

Castro V et al. (2017) also conducted a systematic review and meta analysis of cluster RCT to review the effectiveness of interventions for dengue vector control, using standard entomological indices as measured in cluster randomised controlled trials (CRCTs). Systematic search was conducted from these databases, Medline, Ovid, BVS, LILACS, ARTEMISA, MBIOMED and MEDIGRAPHIC between January 2003 and October 2016. Eligible studies in this review were CRCT of chemical or biological control measures, or community mobilisation, alone or combination; with entomological indices as an endpoint (at least one of three indices; HI, CI and BI. They defined HI as household with larvae or pupae as a proportion of household examined; CI as containers with larvae or pupae as a proportion of containers examined; and BI as containers with larvae or pupae. Comparator was routine dengue control activity. Methodological validity was assessed using Cochrane risk of bias tool. Meta analysis using random effect model assessing the impact on HI, CI and BI were available for interventions from ten studies. Intervention effectiveness was measured as difference (overall risk difference) between intervention and control group at the last point of measurement, for each intervention (chemical, biological, community mobilisation).

The review included 18 studies involving 246 intervention clusters (48,131 interventions household) and 288 control clusters (69,430 controls household) from 13 countries; India, Thailand, Sri Lanka, Cuba, Haiti, Mexico, Guatemala, Nicaragua, Venezuela, Brazil, Uruguay, Ecuador and Colombia. Intervention assessed were chemical control (eight) [temephos, insecticide treated window and door screens or curtain, treated bed nets, deltamethrin lethal ovitraps and *Bti*, deltamethrin treated window curtain and container cover], biological control (one) [copepods or *Bti*] and community mobilisation and participation for dengue prevention (nine) [engagement of local stakeholders, involvement of community in prevention and dissemination, household visits, educational programmes at household and community level, partnership with local services and effort to improve local services], ranged from six weeks to 18 months.

The pooled intervention impact of chemical control on BI was 0.01(95%CI -0.03, 0.05), while that of community participation was -0.13(95%CI -0.22,-0.05). (Figure 12). They found **community mobilisation** (four studies) was **consistently effective in reducing entomological indices; BI, CI and HI with pool RD** as in Table (5). The single biological control had less effectiveness than community mobilisation for HI, BI and CI. While the five studies of chemical control did not show significant overall effectiveness, except for HI. (Table 5)

They concluded community mobilisation programmes as an effective intervention to reduce *Aedes aegypti* entomological indices, and suggested government that relies on chemical control of *Aedes aegypti* to consider adding community mobilisation to their prevention efforts. Better conducted CRCTs of complex interventions, including biological control, are needed as well as trials of all interventions should measure impact on dengue risk. [44 level I]

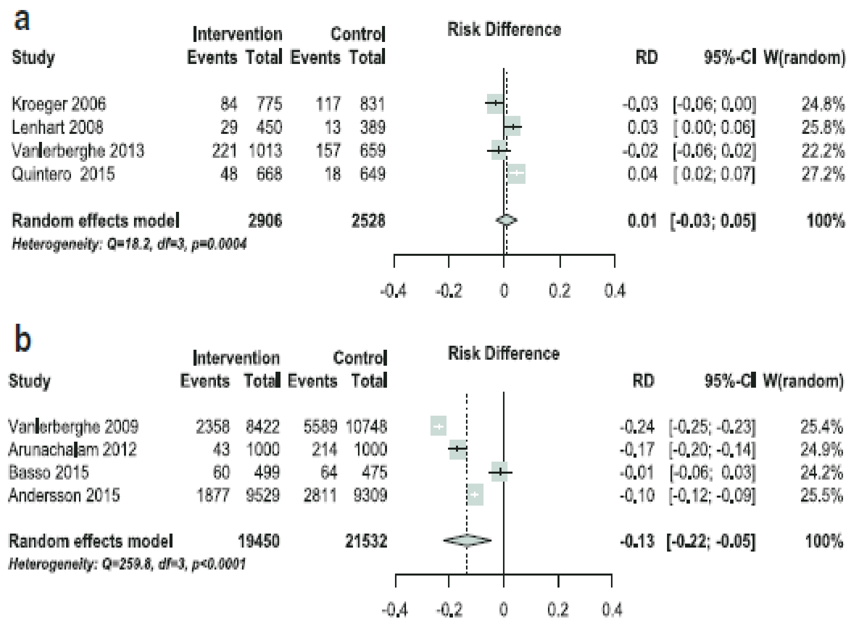

Figure 12: Intervention effect measured by BI for (a) chemical control studies, (b) community participation studies

Table 5: Overall effectiveness of different interventions in SR (Castro et al.2017)

Intervention	Outcome	Pool Risk Difference (95%CI)
Community mobilisation (n=4)	HI	-0.10(95%CI -0.20,0.00)
	CI	**-0.03(95%CI -0.05, -0.01)**
	BI	**-0.13(95%CI -0.22, -0.05)**
Biological (n=1)	HI	-0.02 (95%CI -0.07,0.03)
	CI	**-0.02 (95%CI -0.04,-0.01)**
	BI	**-0.08 (95%CI -0.15,-0.01)**
Chemical (n=5)	HI	**-0.01 (95%CI -0.05,-0.03)**
	CI	0.01 (95%CI -0.01,0.02)
	BI	0.01 (95%CI -0.03,0.05)

Caprara A et al. (2015) conducted a cluster randomised controlled trial (cRCT) to implement a novel intervention strategy in Brazil using an ecohealth approach, and to analyse its effectiveness and costs in reducing *Aedes aegypti* vector density as well as its acceptance, feasibility and sustainability.

In the study, ten randomly selected intervention clusters with ten control clusters (using geographically sampling method) were selected. Standard entomological survey quantified evidence on vector densities. Participatory research facilitated the design and conduct of community-based intervention. Social and anthropological field research (key informant interviews and participatory observations) derived qualitative data about social participation and community empowerment in the intervention clusters.

Pre-intervention entomological survey was conducted in November and December 2012, intervention was developed from January to April 2013 followed by post intervention entomological survey in May 2013. Interventions consisted of a)

Community workshop to empower the community and have a collective responsibility for dengue prevention, b) Involvement of community during clean-up campaign, c) Mobilising school children and elderly regarding dengue prevention, d) Distribution of information, education and communication (IEC) materials; compared to routine vector control. During the intervention period, the process of empowerment-collaboration-mobilization by means of these indicators of community participation by Draper K.(leadership, planning and management, involvement of women, external support and monitoring and evaluation) were analysed. In this study, variation of the HI, CI, BI and PPI (the larval indices) from the dry season (before intervention) to the rainy season (after the intervention) was assessed by means of linear mixed models. Qualitative data were recorded, transcribed and transferred to a central database using NVivo software. Cost items were classified according to the resources consumed (personnel, consumables, transport operating cost and other cost incurred in meetings with community), descriptively analysed and aggregated to calculate total costs and costs per house reached.

They visited a total of 2411 places in both dry and rainy season (2353 household and 58 public space), with 628 tanks covered in the intervention area (vector breeding places). Entomological indices; HI, CI, BI and PPI were increased from the dry season (before intervention) to the rainy season (after the intervention). The increase was significantly higher in the control area, demonstrating the protective efficacy of the intervention, as shown in Table 6.

Table 6: Entomological indices in intervention and control areas, achieved by eco-bio-social integrated intervention (Caprara et al. 2015)

Indicators	Dry season		Rainy season		p value
	Control	Intervention	Control	Intervention	
HI	0.8383	1.2944	3.1664	2.0497	0.02
CI	0.1625	0.1799	0.7157	0.2228	0.02
BI	1.0278	1.5991	4.3158	2.4646	0.01
PPI	0.0104	0.0229	0.0539	0.0292	0.02

They concluded that embedding social participation and environmental management for improved dengue vector control was feasible and significantly reduced vector densities. Such a participatory ecohealth approach offers a promising alternative to routine vector control measures. [45 level II-1]

Another cRCT was conducted by Foster et al. (2015) to examine the effectiveness of applying an integrated community-based approach, comparing with government programs, and to investigate effectiveness and feasibility of scaling up an ecosystem approach to dengue prevention and control. In this study, an integrated intervention strategy (IIS) for dengue prevention, eco-bio-social (integrated community based) comprising of Dengue (elementary school-based dengue education programme (DESE), and clean patio and safe container programme (CPSC) was implemented in 10 intervention clusters from November 2012 to November 2013 in Machala, Ecuador.

The study population consisted of 20 clusters RCT (10 intervention clusters, 10 control clusters), involving 1986 household (4014 intervention residents, 3886 control residents). Existing dengue prevention programmes by National Vector Borne Disease Control Service, MoH served as control treatment (consisted of insecticide-based programme and biolarvicide-based programme). Two stage sampling design using satellite image map generated by Google map was used to determine the study clusters. The main outcome measured was Pupa Per Person index (PPI). Other outcome measures were House Index (HI), Breteaux Index (BI). In this study, social mobilization and empowerment with IIS was monitored. Pre-intervention baseline surveys were done in March 2012 and post-intervention surveys done in November 2013 (both rainy season). Comparative analysis for RCCT was based on data collected through the use of both entomological and household surveys.

They found **eco-bio-social (integrated community based) intervention was effective in reducing both HI (13.0 % versus 1.3%) and BI (29.6% versus 1.7%)** for pre-intervention and post-intervention, observed respectively in their household.

They concluded in the rapidly evolving political climate for dengue control in Ecuador, integration of successful social mobilisation and empowerment strategies with existing and emerging biolarvicide-based government dengue prevention and control programs is promising in reducing PPI and dengue transmission risk in southern coastal communities like Machala. [46 level II-1]

Kittayapong et al. (2012) also conducted a cRCT to demonstrate an application of integrated, community-based, eco-bio-social strategies in combination with locally-produced eco-friendly vector control tools in the dengue control programme, emphasizing urban and peri-urban settings in Chachoengsao province, eastern Thailand.

In this study, three different community settings were selected (Soi Li-Kae, Wannaying and Nueng Kate) and were randomly assigned to intervention and control clusters. The study involved 441 household with pupae per person Index of 0.37 (Intervention cluster) and 448 household with pupae per person Index of 0.38 (Control cluster). Key community leaders and relevant governmental authorities were approached to participate in this intervention programme. Ecohealth volunteers were identified and trained in each study community. They were selected among active community health volunteers and were trained by public health experts to conduct vector control activities in their own communities using environmental management in combination with eco-friendly vector control tools. These trained ecohealth volunteers carried out outreach health education and vector control during household visits. Management of public spaces and public properties, such as solid waste management, was carried out by local municipalities. Entomological surveys were conducted before the intervention and every two months after (May to Nov 2010). Significant reduction in the pupae per person index in the intervention clusters when compared to the control ones was used as a proxy to determine the impact of this programme. Data on acceptance of the vector control measures was collected using a structured questionnaire.

Intervention carried out for six-months were eco-bio-social or ecohealth strategies which comprised of; 1)ecosystem management (garbage and environmental management, provision of piped supply, public land space maintenance), 2) source reduction and social mobilization (removal/reduction of water containers, protection of water containers), and 3)integrated physical and biological methods (applying tight screen covers or lids (MosNet),Mosquito Traps (Mos House®) and portable vacuum aspirator (MosCatch™) and applying biocontrol agent, *Mesocyclops thermocyclopoides* (copepods) or biolarvicide, *Bacillus thuringiensis subsp. israelensis (Bti sacs)).* Routine vector control measure using Abate (temephos) in potential breeding area and fogging to kill adult mosquito were done in the control clusters.

They found at the six-month follow-up, entomological indices decreased in all clusters. **All larval indices (HI, BI and CI), in both treatment and control clusters were significantly lower than at baseline**. Breteau Index (BI) was significantly lower in both treatment (24.46) and control groups (21.49) than the baseline (81.86 and 78.79), respectively. There were no significant differences in HI, CI and BI indices between treatment and control clusters at each surveyed interval. (Table 7)

Table 7: Control measures applied to potential breeding containers and follow-up entomological survey in the treatment (T) and control (C) clusters (Kittayapong 2012)

Items	Baseline		Month 2 follow-up		Month 4 follow-up		Month 6 follow-up	
	T	C	T	C	T	C	T	C
No. of inspected houses	441	448	403	400	332	368	368	335
No. of inspected containers	3,922	3,173	3,572	2,826	2,610	2,341	2,992	2,011
No. of pupa-positive containers	122	109	66	122	31	50	32	43
No. of pupae	648	583	245	970	60	346	42	361
No. of residents	1,758	1,535	1,565	1,535	1,215	1,457	1,485	1,290
House Index (HI)*	37.19	38.84	33.25	32.00	20.41	21.20	11.68	14.03
Container Index (CI)**	9.20	11.19	8.03	9.24	6.30	5.51	3.01	5.38
Breteau Index (BI)***	81.86	78.79	71.22	65.25	49.10	35.05	24.46	21.49
No. of containers applied Bti sacs	1,969		921		522		588	
No. of containers applied copepods	–		347		168		253	
No. of screen net covers applied on containers	943		–		–		–	

*At the six-month follow-up, the HI in both treatment and control clusters was significantly lower than at baseline, *P*=0.000.
** At the six-month follow-up, the CI in both treatment and control clusters was significantly lower than at baseline, *P*=0.002 and *P*=0.001, respectively.
*** At the six-month follow-up, the BI in both treatment and control clusters was significantly lower than at baseline, *P*=0.002 and *P*=0.001, respectively.

They concluded an eco-friendly dengue vector control programme was successfully implemented in urban and peri-urban settings in Thailand, through intersectoral collaboration and practical action at household level, with a significant reduction in vector densities. [47 level II-1]

Another study was conducted by Gurtler et al. (2009) to describe the implemented intervention programme and assess long term effect of vector suppressive action on *Aedes aegypti* indices and incidence of dengue during the 5-year period. The study was based on a before-and-after citywide assessment of *Aedes aegypti* larval indices and the reported incidence of dengue in Clorinda, northeastern Argentina over 2003-2007. Intervention was focal treatment with larvicides of every mosquito developmental site every four months (14 cycles), combined with source reduction and ultra-low-volume insecticide (ULV) spraying during emergency operation.

Total households treated with larvicide were 37,000 (22.2%, SD: 2.8%) (for five-years duration), with mean 193kg (SD 45kg) of temephos applied at each focal cycle. Mean number of positive containers detected at each focal cycle was 738 (SD 418), with average household inspection per cycle of 8,511.They found infestation of water holding container type differed largely among types of container. Large water-storage containers (tanks, barrels, drums for water storage) were the most abundant and infested (cycle 12).

The BI declined from 19.0(baseline) to 4.8(second cycle) and further 2.1(fourteenth cycle). The indices fluctuated and peaked between summer, with variation between neighbourhood. Larval indices decreased more sharply immediately after the control action executed at cycle 1, than at subsequent cycles. Larval indices seldom fall to zero shortly after intervention at the same infested unit (after focal cycle 1 to 7). Monthly HI and BI over the five-years were highly positively correlated (r=0.96,p<0.001). (Table 8).

Table 8: Summary of intervention and larval indices at the preliminary survey and over focal treatment cycles (1 to 14), 2002-2007 (Gurtler et al 2009)

Focal cycle	Date of beginning	Duration (days)	MPI	Number of houses					House index	Breteau index	Number of houses sprayed with ULV
				Inspected	Treated	Closed	Refusing access	Visited			
Preliminary	18/11/2002	25	−3	1808	0	NA	NA	1808	19.5	22.5	0
1	03/10/2003	141	0	7512	3170	2621	724	10857	13.7	19.0	1195
2	08/01/2003	131	5	7822	2842	3213	553	11588	3.7	4.8	623
3	01/05/2004	97	10	7430	2221	2560	328	10318	7.3	9.2	750
4	14/04/2004	79	13	7168	2250	2657	251	10076	8.6	10.6	0
5	07/05/2004	133	16	7021	2040	3013	286	10320	3.3	3.9	227
6	19/11/2004	87	21	7137	2123	2586	289	10012	6.5	8.3	1552
7	17/02/2005	71	24	7414	2314	2674	351	10439	5.2	5.5	688
8	14/06/2005	124	29	8219	2688	3208	566	11993	5.2	6.8	0
9	26/10/2005	128	33	7845	2183	3244	533	11622	4.6	5.8	0
10	16/02/2006	56	36	5587	1833	1644	261	7492	11.7	16.6	426*
11	15/05/2006	99	38	9832	2953	3854	494	14180	6.3	7.9	0
12	24/08/2006	148	41	11484	3538	3604	226	15314	8.6	11.8	0
13	23/01/2007	161	44	12322	3608	3536	381	16239	8.2	12.1	0*
14	26/06/2007	160	47	12366	2925	3697	282	16345	1.8	2.1	0
Total		1631	354	120967	36688	42111	5525	168603			5461

Following multiple regression model, the **BI declined significantly in nearly all focal cycles compared to pre-intervention indices** clustered by neighbourhood, after allowing for lagged effects of temperature and rainfall, baseline BI and surveillance coverage. Table 9.

Table 9: Random-effect multiple regression model of the effect of focal treatment cycles on Breteau Indices (linear model) and house indices (logistic model), relative to cycle 1, 2003-2007

Explanatory variables	House index				Breteau index			
	OR	95% confidence interval		P-value	Coefficient	95% confidence interval		P-value
Mean temperature at lag 4	1.040	1.011	1.071	0.007	0.028	0.014	0.042	0.000
Mean minimum temperature at lag 1	1.054	1.036	1.072	0.000	0.035	0.020	0.050	0.000
Mean rainfall at lag 1	1.023	1.014	1.032	0.000	0.014	0.008	0.020	0.000
Treatment								
Focal 2	0.397	0.262	0.603	0.000	−1.132	−1.540	−0.724	0.000
Focal 3	0.544	0.358	0.828	0.005	−0.834	−1.222	−0.446	0.000
Focal 4	0.994	0.559	1.766	0.983	−0.482	−0.889	−0.074	0.020
Focal 5	0.467	0.255	0.857	0.014	−1.078	−1.483	−0.673	0.000
Focal 6	0.419	0.308	0.569	0.000	−0.905	−1.309	−0.501	0.000
Focal 7	0.269	0.183	0.397	0.000	−1.343	−1.740	−0.945	0.000
Focal 8	0.823	0.403	1.677	0.591	−0.811	−1.215	−0.406	0.000
Focal 9	0.345	0.201	0.592	0.000	−1.263	−1.661	−0.866	0.000
Focal 10	0.990	0.700	1.400	0.955	−0.012	−0.573	0.334	0.606
Focal 11	0.731	0.468	1.143	0.169	−0.354	−0.671	−0.037	0.029
Focal 12	0.793	0.461	1.365	0.403	−0.359	−0.757	0.039	0.077
Focal 13	0.640	0.334	1.228	0.180	−0.693	−1.115	−0.270	0.001
Focal 14	0.129	0.076	0.218	0.000	−1.882	−2.318	−1.445	0.000
Baseline larval index	1.008	0.983	1.033	0.553	0.374	0.254	0.494	0.000
Surveillance coverage	0.522	0.345	0.789	0.002	−0.141	−0.560	0.279	0.512

The authors concluded that control intervention exerted significant effect on larval indices, but failed to keep them below target level during every summer, and achieved sustained community acceptance. For further improvement, a shift is needed towards a multifaceted program with intensified coverage and source reduction efforts, lids or insecticide-treated covers to water storage containers, and a broad social participation aiming at long term sustainability. [41] level II-2

The effectiveness of various interventions on entomological indices measured by BI is summarised in the Table 10 below.

Table 10: Summary effectiveness of various control interventions on BI

Study	Intervention	Effect measure
Erlanger et al (2008) SR RCT & observational studies	Chemical control (outdoor adulticide) (3 studies)	pool RE = 0.24 (95%CI 0.05,1.19)
	Environmental Management (Environmental modification, environmental manipulation, modification of human habitat or behavior to reduce human-vector contact) (9 studies)	**pool RE = 0.71 (95%CI 0.55,0.90)**
	IVM (EM & chemical control) (11 studies)	**pool RE = 0.33 (95%CI 0.30,0.79)**
Castro et al (2017) SR of cRCT	Chemical control (5 studies)	pool RD = 0.01 (95%CI 0.05,1.19)
	Community participation (4 studies)	**pool RD = -0.13 (95%CI -0.22,-0.75)**
Caprara et al (2015) cRCT, Brazil	Ecohealth approach (community empowerment for dengue prevention, clean up campaign, mobilizing school children & elderly, distribution of education materials)	1.03 vs 1.59 (dry season) 4.32 vs 2.46 (rainy season) p<0.02
Foster at el (2015) cRCT, Ecuador	Integrated community based [(eco-bio-social) integrated intervention strategy for prevention, DESE, CPSC programme) (1 year)	29.6 vs 1.7 (pre vs post intervention)

Kittayapong et al (2012) cRCT, Thailand	Eco-bio-social strategies (ecosystem management, source reduction & social mobilization, integrated physical and biological methods – screen cover, mosquito traps, portable vacuum, *Bti* and *mesocyclops*)	Treatment vs control; 24.46 vs 21.49 (6 months) 81.86 vs 78.79 (baseline)
Gutler et al. (2009) cohort, Argentina	Focal treatment with larvicides of every mosquito developmental site every four months (14 cycles), combined with source reduction and ultra-low-volume insecticide (ULV) spraying during emergency operation.	19.0 (baseline) 4.1 (cycle - 2) 2.1 (cycle - 14)
Vanlerberghe et al. 2010 cRCT	Community based environmental modification, larvicide, water cover, social mobilisation (In Bowman et al (2016))	**0.48* (95%CI 0.26,0.89)**
Castro et al. 2012 cRCT	Community based clean up, social mobilisation, education, inspection (In Bowman et al (2016))	0.65***** (95%CI 0.52,0.81)
Arunachalam et al. 2012 cRCT	Community based environmental management, water covers, social mobilisation, clean up (In Bowman et al (2016))	**-4.66#** **(95% CI -5.89,-3.43)**

RE=relative effectiveness, RD=risk difference

* rate ratio   # mean difference   ^odds ratio

- **Container Index**

Bowman et al. (2016) reported that community based combined intervention significantly reduced CI with mean difference of -12.30 (95%CI -17.36,-7.24) (Table 11).

Table 11: Effectiveness of community based combined intervention for CI

Reference	Design	Intervention	Mean difference (95%CI)
Arunachalam et al. 2012	cluster randomised trial	Community based clean up, social mobilisation, education, inspection	-12.30 (-17.36,-7.24)

Insecticide treated curtains however did not significantly reduced the mean difference for CI, (one study), compared to control (MD=0.24;95%CI -0.17, 0.65).(Figure 3). [39 level II-1]

In the review by Erlanger et al. (2008) for biological control, the organisms used were the following; copepods (*Mesocyclops spp*)(3), fish (4), predatory insect larvae (*Toxorhynchites spp*)(2),*Crocothemis spp* (1). Meta analysis for biological control against dengue vector measured by Container Index (9 studies), demonstrated the pooled RE of 0.18 (95%CI 0.07, 0.44).(Figure 13).

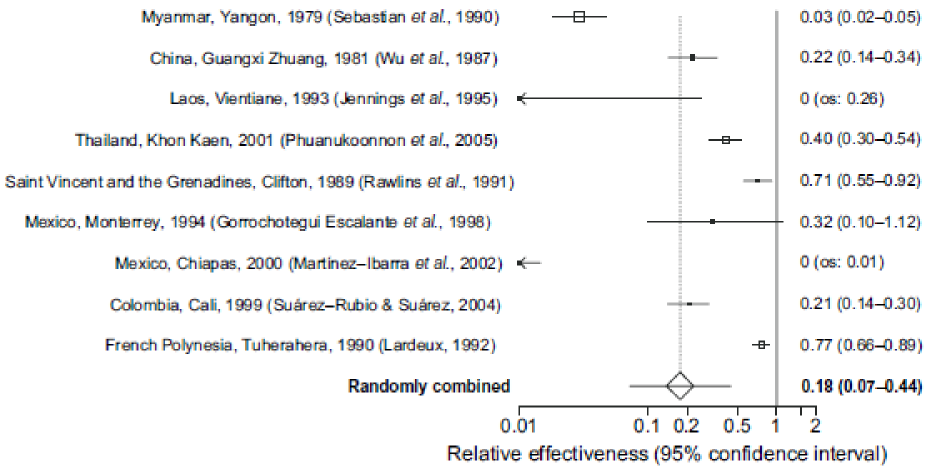

Figure 13: Performance (Relative Effectiveness) of biological control against dengue vectors measured by Container Index

Erlanger et al. (2008) in his review found for environmental management, the most used method were removal of unused water vessels and covering of water containers. They found the pooled RE for environmental management was 0.43 (95%CI 0.31, 0.59) measured by CI in a meta analysis from 10 studies. (Figure 14).

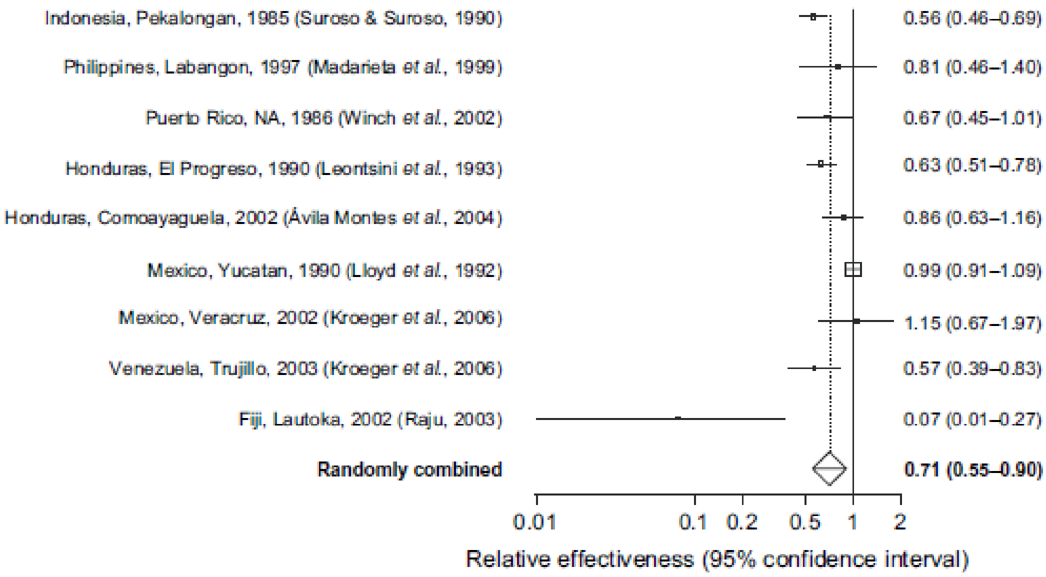

Figure 14: Performance (Relative Effectiveness) of environmental management against dengue vectors measured by Container Index

In the review by Erlanger et al. (2008), they found IVM (combination of EM and chemical control) had the pooled RE of 0.17(95%CI 0.02,1.28) measured by HI (9 studies). (Figure 15). [20 level II-1]

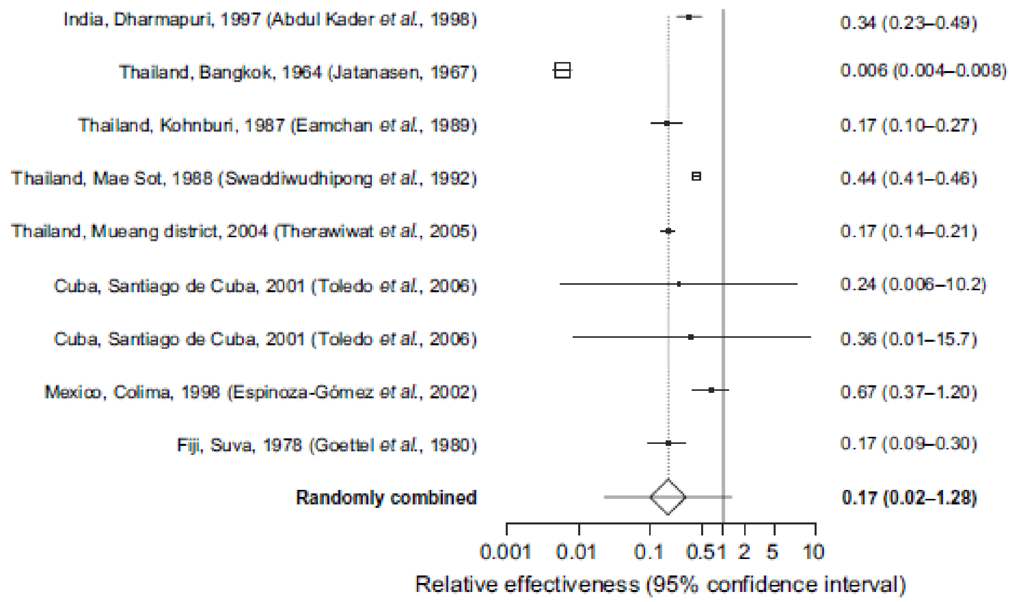

Figure 15: Performance (Relative Effectiveness) of IVM (environmental management and chemical control) against dengue vectors measured by Container Index

In the review by Castro et al. (2017), community participation intervention showed the most effective impact with overall intervention impact for CI of -0.03(95%CI -0.05,-0.01) for community participation intervention and 0.01 (95%CI -0.01, 0.02) for chemical control. The single cRCT of biological intervention reported an impact of -0.02(95%CI -0.04,-0.01) on the CI. (Figure 16). [44 level II-1]

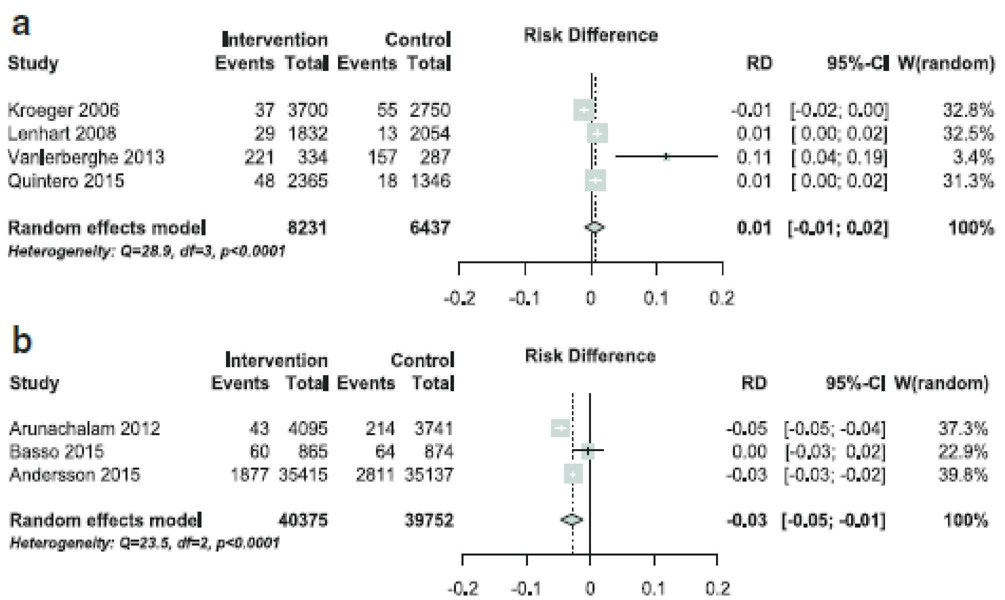

Figure 16: Intervention effect measured by Container Index; for (a) chemical control studies, (b) community participation studies

Caprara et al. (2015) in the cRCT in Brazil found entomological indices, CI increased from the dry season (before intervention) to the rainy season (after the intervention). The increase was significantly higher in the control area, demonstrating the protective efficacy of the intervention, as shown in Table 6. [45 level II-2]

Kittayapong et al. (2012) in the cRCT conducted in Thailand, found the application of integrated, community-based, eco-bio-social strategies in combination with locally-produced eco-friendly integrated physical and biological control tools had significantly reduce CI in both treatment (3.01) and control clusters (5.38) than at baseline (9.20 and 11.19, respectively). There were no significant differences in CI index between treatment and control clusters at each surveyed interval. (Table 12). [47 level II-1]

The effectiveness of various interventions on entomological indices measured by CI is summarised as below.

Table 12: Summary effectiveness of various control interventions on CI

Study	Intervention	Effect measure
Erlanger et al. (2008) SR of RCT & observational studies	Biological control (*copepods*, fish, predatory insect larvae, *crocothemis sp*) (9 studies)	pool RE = 0.18 (95%CI 0.07,0.44)
	Environmental Management (Environmental modification, environmental manipulation, modification of human habitat or behavior to reduce human-vector contact) (10 studies)	**pool RE = 0.43 (95%CI 0.31,0.54)**
	IVM (EM & chemical control) (9 studies)	**pool RE = 0.17 (95%CI 0.02,1.28)**
Castro et al. (2017) SR of cRCT	Chemical control (4 studies)	pool RD = 0.01 (95%CI -0.01,0.02)
	Community participation (3 studies)	**pool RD = -0.03 (95%CI -0.05,-0.01)**
Kittayapong et al. (2012) cRCT, Thailand	Eco-bio-social strategies (ecosystem management, source reduction & social mobilization, integrated physical and biological methods – screen cover, mosquito traps, portable vacuum, *Bti* and *mesocyclops*)	Treatment vs control; 3.01 vs 5.38 (6 months) 9.20 vs 11.19 (baseline)
Arunachalam et al. 2012 cRCT	Community based environmental management, water covers, social mobilisation, clean up mobilisation (In Bowman et al.(2016))	-12.30* (-17.36,-7.24)

RE=relative effectiveness, RD=risk difference, *mean difference

- **House Index**

Bowman et al. (2016) also reported that community based combined intervention significantly reduced HI with rate ratio of 0.49(95%CI 0.27, 0.89) and mean difference of -17.10(95%CI -22.16,-12.04). In the similar review, the use of fogging, source reduction, larviciding and house inspection was found to significantly reduce the odds of detecting increased larval densities measured by HI, when compared to baseline with OR of 0.13(95%CI 0.08, 0.22)]. Likewise, it was reported that community based environmental management, source reduction, larviciding, adulticiding, education and water covers significantly reduced HI with MD of -2.14 (95%CI-3.72,-0.56) (Table 13).[39 level II-1]

Table 13: Effectiveness of community based combined intervention for HI (in Bowman et al. 2016)

Reference	Design	Intervention	Effect measure (95%CI)
Vanlerberghe et al. 2010	cluster randomised trial	Community based environmental modification,larvicide,water cover, social mobilisation	**0.49*** **(0.27,0.89)**
Arunachalam et al. 2012	cluster randomised trial	Community based clean up, social mobilisation, education, inspection	**-17.10#** **(-22.16,-12.04)**
Gurtler et al. 2009	pre and post intervention study	Larvicide, source reduction, ULV fogging, house inspection	**0.13^** **(0.08, 0.22)**
Baly et al. 2009	controlled clinical trial	Community based environmental management, source reduction, larviciding, adulticiding, education, water cover	**-2.14#** **(-3.72,-0.56)**

* rate ratio   # mean difference ^odds ratio

Insecticide treated curtains however did not significantly reduced the pooled mean difference for HI, (two studies), compared to control (MD= -10.58; 95%CI - 32.22, 11.05). [39 level II-1]

Erlanger et al. (2008) found the pooled RE for environmental management measured by HI was 0.43(95%CI 0.31, 0.59) (from ten studies).(Figure 17). While for IVM (EM and chemical control), the pooled RE was 0.12(95%CI 0.02, 0.62) measured by HI (from nine studies). (Figure 17). [20 level II-1]

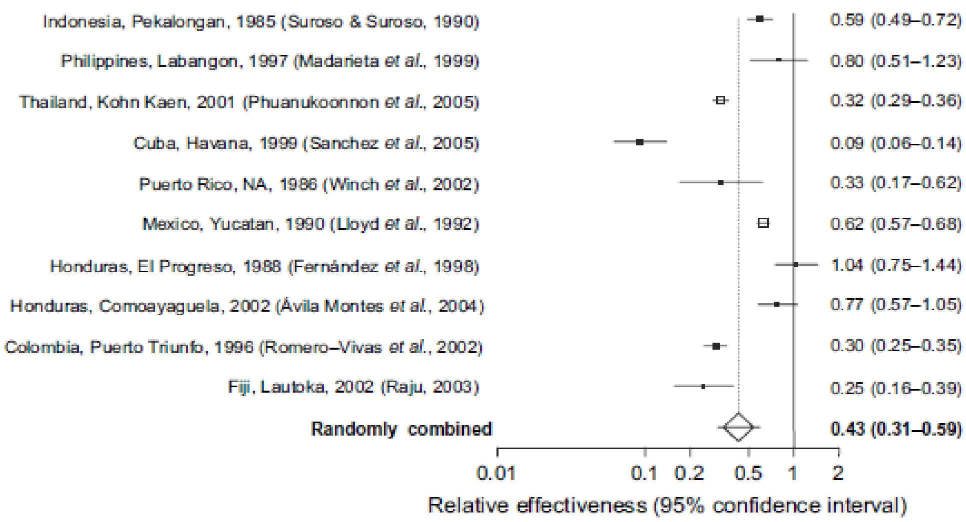

Figure 17: Performance (Relative Effectiveness) of environmental management against dengue vectors measured by House Index

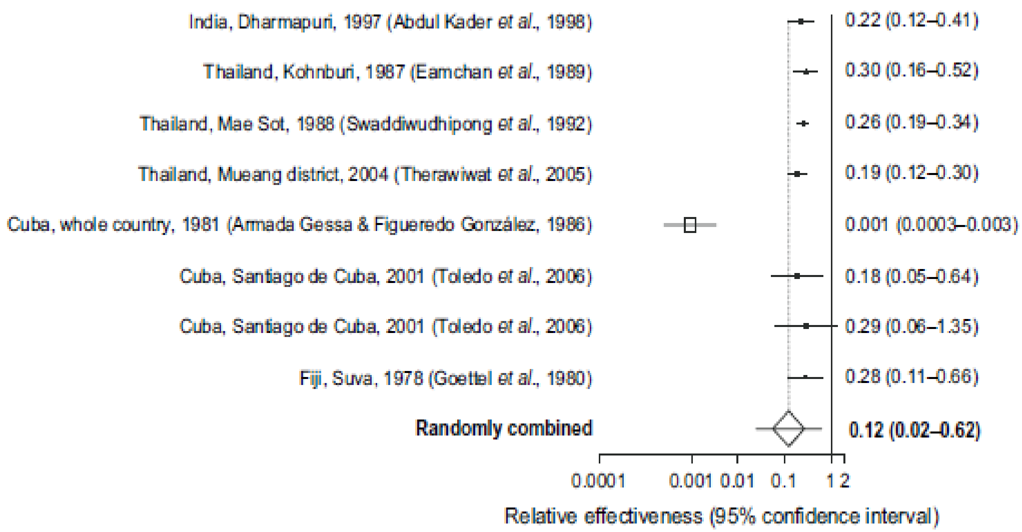

Figure 18: Performance (Relative Effectiveness) of IVM (environmental management and chemical control) against dengue vectors measured by House Index

In the review by Castro et al. (2017), the overall intervention impact assessment for HI were -0.01(95%CI -0.05, 0.03) for chemical control, and -0.10(95%CI -0.20, 0.00) for community participation, significant impact of community participation on HI. (Figure 19). [44 level II-1]

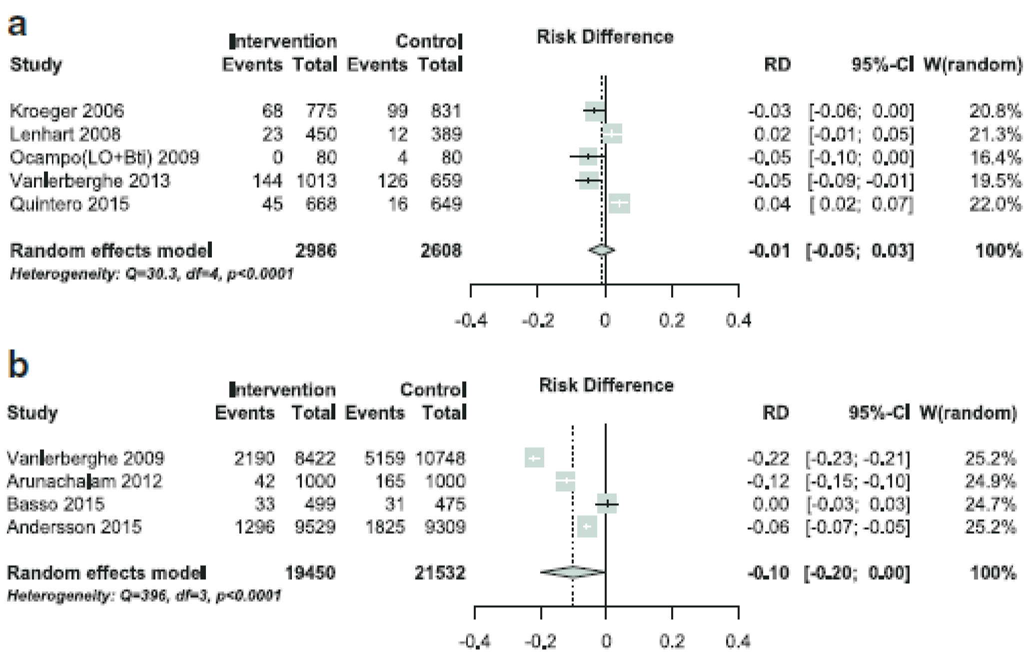

Figure 19: Intervention effect measured by Household Index for (a) chemical control studies (b) community participation studies

Caprara et al. (2015) in the cRCT in Brazil found entomological indices; HI increased from the dry season (before intervention) to the rainy season (after the intervention). The increase was significantly higher in the control area (p=0.02), demonstrating the protective efficacy of the intervention, as shown in Table 6. [45 level II-2]

The study by Gurtler et al. (2009), as described above which was based on a before-and-after citywide assessment of *Aedes aegypti* larval indices and the reported incidence of dengue in Clorinda, northeastern Argentina over 2003-2007 with these interventions; focal treatment with larvicides of every mosquito developmental site every four months (14 cycles), combined with source reduction and ultra-low-volume insecticide (ULV) spraying during emergency operation found the HI declined sharply from 13.7% (baseline) to 3.7% (second cycle) and further to 1.8 (fourteenth cycle). (Table 8). [41 level II-2]

Kittayapong et al. (2012) in the cRCT conducted, found the application of integrated, community-based, eco-bio-social strategies in combination with locally-produced eco-friendly integrated physical and biological control tools had significantly reduce HI in both treatment (11.68) and control clusters (14.03) than at baseline (37.19 and 38.84, respectively). There were no significant differences in CI index between treatment and control clusters at each surveyed interval. (Table 7) [47 level II-1]

In the review by Bowman et al. (2016), it was reported that the use of fogging, source reduction, larviciding and house inspection reduced the odds of detecting increased larval densities, with HI [OR=0.13(95%CI 0.08, 0.22)] when compared to baseline.[39 level II-1] The overall effectiveness of various interventions on entomological parameter measured by HI, is illustrated in the Table 14 below.

Table 14: Summary effectiveness of various control interventions on HI

Authors	Intervention	Effect measure
Erlanger et al. (2008) SR	Environmental Management (Env.modification, env manipulation, modification of human habitat or behavior to reduce human-vector contact)	**pool RE = 0.49 (95%CI 0.30,0.79)** 10 studies
	IVM (EM & chemical control)	**pool RE = 0.17 (95%CI 0.02,1.28)** 9 studies
Castro et al (2017) SR of cRCT	Chemical control	pool RD = -0.01 (95%CI -0.05,0.03) 5 studies
	Community participation	**pool RD = -0.1 (95%CI -0.2, 0.0)** 4 studies
Kittayapong et al (2012) cRCT, Thailand	Eco-bio-social strategies (ecosystem management, source reduction & social mobilization, integrated physical and biological methods – screen cover, mosquito traps, portable vacuum, Bti and mesocyclops)	Treatment vs control; 11.68 vs 14.03 (6 months) 37.19 vs 38.84 (baseline)
Gutler et al. (2009) cohort, Argentina	focal treatment with larvicides of every mosquito developmental site every four months (14 cycles), combined with source reduction and ultra-low-volume insecticide (ULV) spraying during emergency operation.	13.7 (baseline) 3.7 (cycle - 2) 1.8 (cycle - 3) **0.13^ (95%CI 0.08, 0.22)**
Vanlerberghe et al. 2010 cRCT ^^	Community based environmental modification, larvicide,water cover, social mobilisation	**0.49* (95%CI 0.27,0.89)**
Arunachalam et al. 2012 cRCT ^^	Community based clean up, social mobilisation, education, inspection	**-17.10# (95%CI -22.16,-12.04)**
Baly et al. 2009 ^^	Community based environmental management, source reduction, larviciding, adulticiding, education, water cover	**-2.14# (95%CI -3.72,-0.56)**

RE=relative effectiveness, RD=risk difference

* rate ratio   # mean difference   ^odds ratio   ^^in Bowman et.al 2016

- **Combination of entomological indices (BI, CI and HI)**

Almuhandis N et al. (2011) conducted a systematic review to investigate the relative effectiveness (RE) of different educational messages embedded in a community-based approach on the incidence of *Aedes aegypti* larvae using entomological measures as outcomes. Systematic search was done from these databases; Medline, Embase, Web of Science, Cochrane Library, with search done up to March 2010. Primary outcome was entomological measures; BI specifies the number of containers with *Aedes sp* larvae per 100 houses, CI represents percentage of water container positive for aedes sp larvae, and HI gives percentage of houses with water containers holding immature *Aedes sp*. Primary effect measure was relative effectiveness (RE); ratio between entomological index in intervention and control group (the more effective the intervention, the lower the RE).

Included studies were only study with educational element to their intervention, defined as any community based intervention that had element where members of public were given information intended to change behavior. Inclusion criteria were control of dengue, investigate effect of educational intervention alongside other control approach, quantitative outcomes and community based. A total of 22 studies were finally included from these regions; South America (11),South East Asia (9), Fiji & French Polynesia (2). Intervention assessed was educational messages (vary whether or not intervention communities received other intervention) alongside a standard control programme. They found these type of interventions; educational and chemical intervention (9), educational and other than chemical control (8).

Estimated correlation of the different entomological indices (CI, BI and HI) in the study showed there was high correlation between CI and HI for the RE, whreas moderate for BI and CI, as well as BI and HI as below:-

- CI-HI:Correlation of 0.97
- BI-CI: Correlation of 0.68
- BI-HI: Correlation of 0.66

They concluded that combining the different entomological indices was valid. The combined **relative effectiveness, RE** for educational, chemical and other interventions against the entomological indices was 0.25(95%CI 0.17,0.37) with significant heterogeneity, Cochran's Q=1254, p<0.001. (Figure 20). Following that meta regression was conducted in the attempt to explore the heterogeneity. They found that 60% of between study variance could be explained by; 'whether or not studies used historic/contemporary control' and 'time from intervention to assessment'.[48 level II-1]

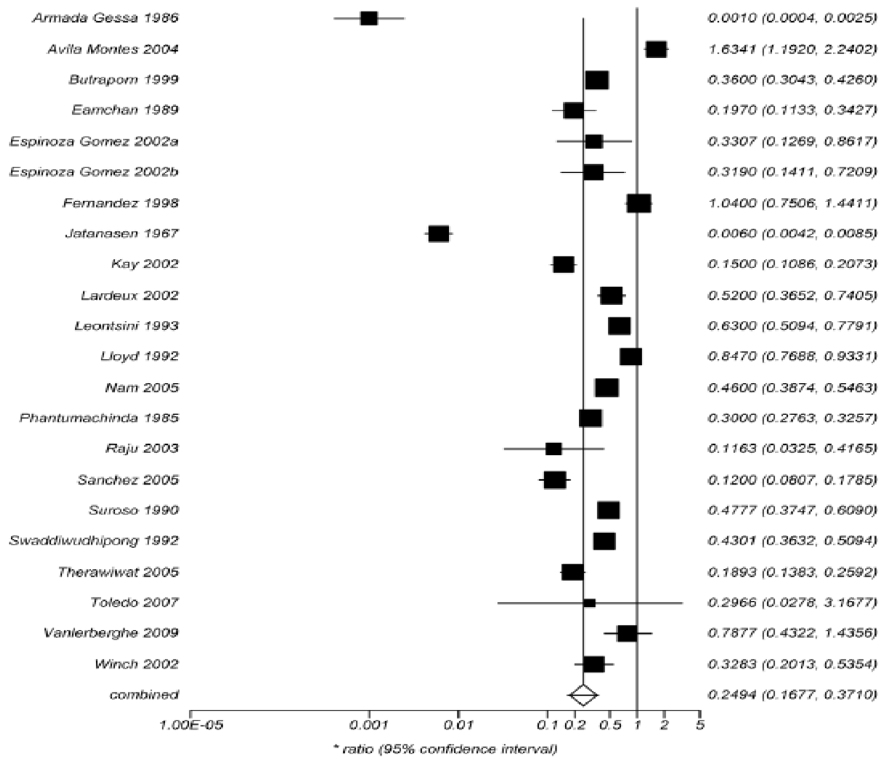

Figure 20: Performance of educational, chemical and other interventions against entomological indices

- **Pupae per person index (PPPI)**

Castro et al. (2017) in their review found significant impact of cRCT of biological control using either *copepods* or *Bti* on pupae per person index in intervention than control clusters at all time point up to six months, after the baseline (one study). [44 level II-1]

In another review by Bowman et al. (2016), insecticide treated curtains did not significantly reduced the mean difference for PPPI (one study), (MD=0.19;95%CI-0.37,0.75).(Figure 3). [39 level II-1]

Foster et al. (2015) in the cRCT conducted found eco-bio-social (integrated community based) intervention was effective in significantly reducing overall PPI values in intervention cluster compared to control cluster. (Table 15) [49 level II-2]

Table 15: Overall PPI result following eco-bio-social intervention (in Foster et al. 2015)

Item	PPI(2012)	PPI(2013)	%Change	p value	Person	No. pupa (2012)	No. pupa (2013)
Total	0.668	0.252	-62.3%	<0.001	7900	5278	1988
Intervention	0.524	0.080	-85.1%		4014	2102	314
Control	0.817	0.353	-47.2%		3886	3176	1674

Kittayapong et al. (2012) in the cRCT conducted, found the application of integrated, community-based, eco-bio-social strategies in combination with locally-produced eco-friendly integrated physical and biological control tools had significantly reduce the mean PPPI in the treatment and control area, 0.19

versus 0.73 (p=0.024) and 0.05 versus 0.26 (p=0.019) in July and September,during the peak transmission season respectively. [47 level II-1]

- **Ovitrap positivity**

The combination of interventions (clean up campaign, with indoor residual spraying and larviciding) significantly reduced ovitrap positivity with MD of -10.30(95%CI-12.80,-7.80), as reported in systematic review by Bowman et al. (2016). [39 level II-1]

In the pre-post intervention study by Kittayapong et al.(2006) in eastern Thailand, a total of 406 lethal ovitraps were distributed in the treatment village. The study demonstrated that the percentage of ovitraps that contained *Aedes* eggs when traps were first placed among natural breeding sites (66.3%) decreased from 49.6% after the first application to 10.4% at the termination of the study (after 71 weeks). [42 level II-2]

- **Size of population covered and duration**

Erlanger et al. (2008) in their systematic review found IVM (EM and chemical control) had the largest number of population covered (median population size of 12,450; ranged from 210 to 9,600,000. In contrast, the smallest number of people covered with intervention was control using biological methods (median population size of 200, ranged from 20 to 2500. The shortest duration of intervention was using biological intervention (3.25 months), and the longest was IVM [using EM combined with biological control (20.5months)]. (Table 16). [20 level II-1]

Table 16: Population size covered and duration of different dengue vector control intervention

Vector control intervention	Duration of intervention (months)-median	Population covered - median
Chemical	4	2400
Biological	3.25	200
Environmental management	7	3080
IVM (EM and chemical control)	12	12,450
IVM (EM and biological control)	20.5	14,080

- **Performance of control strategies**

Lima EP et al. (2015) conducted a systematic review with meta analysis to identify the most effective vector control strategies and the factors that contributed to the success or failure of each strategy. Systematic search was done from 12 databases from 1974 to December 2013. Intervention assessed was the use of any chemical, physical, biological or integrated action against A aegypti, regardless of the formula, concentration, form of application, target stage of the mosquito and duration of treatment. A total of 26 studies were included from 15 countries, comprising of cluster randomized control trial (6), non randomized controlled trial (16) and pre-post intervention studies (4). They found these intervenntions; Biological (5), Chemical (5), Mechanical (3), and integrated strategies (13) with time interval of intervention ranging from two weeks to 72 months.

The biological control were fish (three species), crustaceans, aquatic insects, bacteria based larvicide (*Bacillus thuringiensis vas israelensis (Bti)).* While, chemical control consisted of pyrethroids, organophospates, benzoylureas, phenyl ether, thioridazine. Physical/mechanical control encompassed regular cleaning of containers, container covers and collecting eggs in ovitraps. Integrated strategies consisted of physical control, community participation (education, elimination of breeding sites), chemical or biological insecticides added to ovitrap, or impregnated in curtains, bednets or covers.

Table 17: Performance analysis of different control strategies (n=22)

Statistics	Biological	Chemical	Integrated	Global
N	5	5	12	22
Chi-square	72.507	52.270	140.035	277.339
p	<0.0001	<0.0001	<0.0001	<0.0001

They found all category of intervention contributed significantly to the control of *A aegypti* (p<0.0001), with integrated intervention showed the greatest impact. While chemical control alone showed the least performance. (Table 17). They concluded the most effective method was the integrated approach, considering the influence of eco-bio-social determinants in the virus-vector-man epidemiological chain, and community involvement, starting with community empowerment as active agents of vector control. [4 level II-1]

- **Sustainability of control programme**

Kay BH et al. (2010) conducted a cross sectional with cost analysis study to see whether or not the community-based dengue control programme represent effective long term solution for the prevention of dengue, and to evaluate if the 1998 - 2000 program was still being maintained seven years later in 2007.

Earlier, a new community-based mosquito control introduced that resulted in the elimination of Aedes aegypti in 40 of 46 communes in northern and central Vietnam. Subsequently, in 2007 and 2008, Nam Dinh and Khanh Hoa province in Northern and Central Vietnam, respectively were revisited. The Nothern Vietnam site consisted of North project commune (NPC), North extended commune (NEC) and North control commune, while the Central Vietnam site consisted of Central project commune (CPC), Central extended commune (NEC) and Central control commune (CCC).

Previously published sustainability framework was used to compare 13 criterias from Tho Nghiep commune in Nam Dinh (Northern Vietnam) where the local community had adopted the community-based project model using Mesocyclops from 2001. In Khanh Hoa (Central Vietnam) province, the 2008 data at Ninh Xuan commune (project completion in 2003) were compared with untreated control (Ninh Binh), where few control activities had been undertaken and used as benchmark. Both qualitative and quantitative methods were used in this study. Several focus group discussions (head of households, collaborators, village health workers) and in-depth interview (26 key informants:

project managers, community project offices, project officers from provincedistrict, communal committee representative and heads of schools) were conducted.KAP survey was carried out to household representatives in whom the entomological survey was conducted.

Sustainability assessment was measured in scores; level of sustainability was scored using a standard five-interval rating system (1 to 1.5 = regressive, 1.5 to 2.5 = not sustained, 2.5 to 3.5 = moderately sustained, 3.5 to 4.5 = well-sustained, and 4.5 to 5 = highly sustained). The 13 criterias used in the scoring were grouped under three headings;

a) Maintenance of health benefits achieved through the initial project,
- New dengue fever (DF) cases
- Entomological indices
- Number of containers for aedes
- KAP of householders

b) Continued delivery of project activities
- Continued activities of collaborators on DF control
- Continued placement of Mesocyclops in large water container
- Continued elimination of Aedes breeding sites
- Continued activities of school/social organisation
- Continued functioning of reporting system

c) Long-term capacity building in the recipient community.
- Human resource development for dengue control
- Maintaining budget allocated for dengue control
- Maintaining diverse, inclusive citizen participation in dengue control
- Maintain leadership base for dengue control

For sustainability of programme, they found at NPC, there was only one disparity in the ratings given by the two researchers, which resulted in sustainability scores of 4.38 and 4.46 of 5.00 (mean = 4.42, well sustained). Small differences in 6 of 13 scores for NEC were observed, resulted in sustainability scores of 3.92 and 3.46 of 5.00 (mean = 3.69, well-sustained), whereas the rating for CPC was 4.20 (well-sustained). This resulted in well sustained classifications for all communes. They concluded the three communes where the above community-based strategy had been adopted were rated as well-sustained. [50 level III]

6.3 SAFETY

There was no retrieveable evidence on safety of IVM for *Aedes* control.

6.4 COST EFFECTIVENESS

There were five retrieavable evidence on the cost-effectiveness of IVM for *Aedes* control, of which three were cost-effectiveness analysis (CEA), and the remaining were cost analysis.

Mendoza-Cano O et al. (2017) conducted a cost-effectiveness analysis to evaluate cost-effectiveness analysis of three different strategies: community participation, ULV spraying and the combination of both in Colima, Mexico. A RCT took place from February 2008 to August 2008 in Colima, Mexico using multistage cluster sampling, whereby municipalities were grouped into three locations according to geographical area. Eight clusters and ten houses were randomly selected. Final study population was 407 involving four blocks. There were four groups, group A (community participation) were given printed material, random group visit, integration of discussion group, game and promotion programme, group B [Ultra-low volume (ULV)] given Permethrin and pipronyl butoxide (11.1g active ingredient/ hectare), group AB (given both interventions) and control (neither campaign nor ULV). Primary outcome of interest were dengue cumulative incidence and DALY's avoided. Incidence rate were calculated, rate ratio was estimated using logistic regression.

Cost-effectiveness approach (direct cost/DALYs avoided) was used to evaluate the implemented interventions.Direct costs associated with each intervention were also computed. Dengue rates were used to evaluate the efficacy of each intervention using the number of laboratory-confirmed incident cases after the follow-up (seven months). DALY was calculated based on 2008 projections from National Population Council.

They found the direct cost ($USD) for each group was; A (27,393.18), B (31,170.47), A and B (58,170.47), and C (12,979.26). Group A (community participation) had the lowest cost when compared with control group, and the highest direct costs showed were from group AB.

Table 18: Efficiency & effectiveness of vector-control interventions

Group	Cases tested/positives	Incidence[a]	Incidence treated by Control [b]	Efficiency [c]	Effectiveness [d]
A	23/4	17.4% (12.6-24)	0.58	0.42	6.93
B	175/25	14.3%(9.3-19.3)	0.47	0.53	6.97
AB	146/20	14.4% (9.4-19.2)	0.48	0.53	5.61
C	63/19	30.2% (20-40)	1.00	0	0

[a] cumulative incidence [b] incidence treated by control = incidence ratio treatment/control
[c] efficiency = 1-incidence treated by control [d] avoided DALY (disability adjusted life year)

They also found the incidence of the vector-borne disease was similar between groups B (ULV) and AB (both interventions). The highest efficiency and effectiveness estimates were observed in group B (ULV). (Table 17). However, the cost-effectiveness balance showed that strategy of community participation (A) was more cost-effective ($3952.84 per DALY avoided).The cost effectiveness balance associated with the interventions per DALY avoided is illustrated in Table 19 below.

Table 19: Cost-effectiveness balance, Mendoza-Cano O et al. (2017)

Group	Intervention	Cost ($USD) per DALY avoided
A	Community participation	3952.84
B	Ultra-low volume	4472.09
AB	Both community participation and ULV	10,439.15
C	Control	-

They suggested that efforts to improve community participation in vector control and ULV-spraying alone are cost-effective and may be useful to reduce the vector density and dengue incidence. [51]

Luz PM et al. (2011) also conducted a cost-effectiveness analysis to estimate the effect of different insecticide-based vector control strategies on health and health economic outcomes in Brazil. In this study, a dengue transmission model was developed, that extends the previous mosquito model to include human population dynamics and dengue transmission. The mosquito model includes seasonality and population genetics of insecticide-resistance evolution. The model parameters were set with ecological and biological data specific to *Aedes aegypti*. The effect of vector control was assessed for a 5-year period. Health outcomes (dengue burden) were measured using DALYs (DALYs lost). Analysis was done from a societal perspective. Costs were expressed in 2009 USD. Costs and DALYs were discounted at a yearly rate of 3%.CEA estimating incremental cost-effectiveness ratio of all 43 vector control strategies were calculated, including strategies for adult and larval control, at **varying efficacies** (high, medium and low) and **yearly application frequencies** (one to six applications). Comparative value was measured in $ per DALY saved during the 5-year vector control assessment period. The Brazil-specific thresholds of $24660 per DALY saved for a cost-effective intervention, and $8220 per DALY saved for a very cost-effective intervention, based on criteria of the WHO Commission of Macroeconomics and Health. Probabilistic sensitivity analysis and threshold analysis were done to examine the effect of parameter uncertainty on the results. Cost effectiveness acceptability curves were used to depict the level of uncertainty surrounding cost effectiveness estimates at different society's willingness to pay for an additional DALY saved.

Two forms of vector control were analysed, adult and larval control; consisted of one to six applications every year. Combination strategies were also assessed. Thus including no vector control, a total of 43 vector control strategies were considered. Larval control persist in environment for two months during which the effectiveness wanes, adult control with ULV insecticide has immediate effect lasts for one day. A **range of efficacies** was explored; high efficacy (90% mortality), medium-efficacy (60% mortality) and low efficacy (30% mortality).

They found for the entire five-year period, expected dengue burden was 1133 DALYs lost per million populations. The average annual dengue burden was 227 DALYs lost per million populations.

The study found in term of larval control for the entire 5-year period, three applications of high-efficacy larval control every year reduced the dengue burden the most; resulting in 829 DALYs lost per million individuals. One or more application of high efficacy larval control reduced the dengue burden during the first two years. Three or more applications of high efficacy larval control reduced the expected annual dengue burden to below 14 DALYs lost per million population. (Figure 21).

Meanwhile, for adult control, six applications of high-efficacy adult control every year reduced the dengue burden the most; resulting in 248 DALYs lost per million individuals for the entire five-year period. Three or more applications of high efficacy adult vector control reduced dengue burden for up to four years.(Figure 22).

Of the combined intervention strategies, one high-efficacy larval control application and five low-efficacy adult control applications reduce the dengue burden to the greatest extent; 733 DALYs lost per million individuals during the five-year period. (Figure 23). Of all vector control strategies, **the strategy that most substantially reduce the number of DALYs lost per million populations during the 5-year period was six applications of high-efficacy adult vector control**.

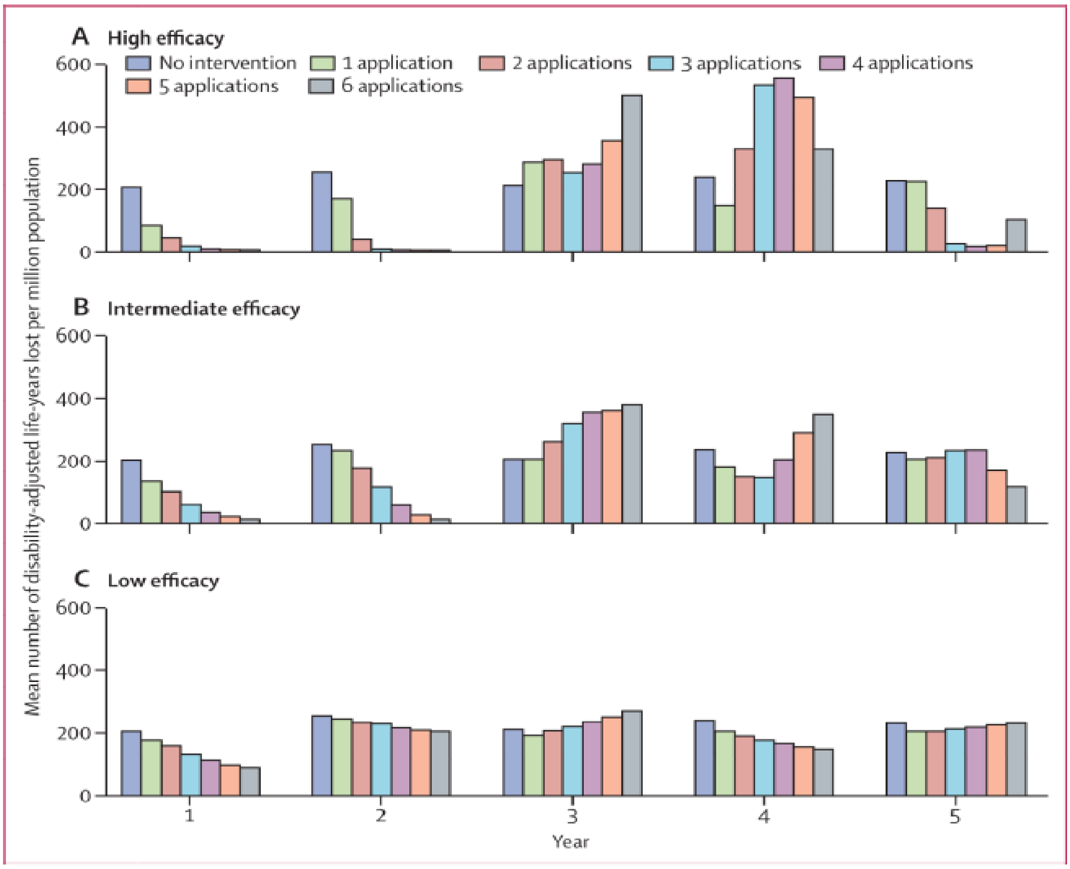

Figure 21: Effect of larval control on dengue burden

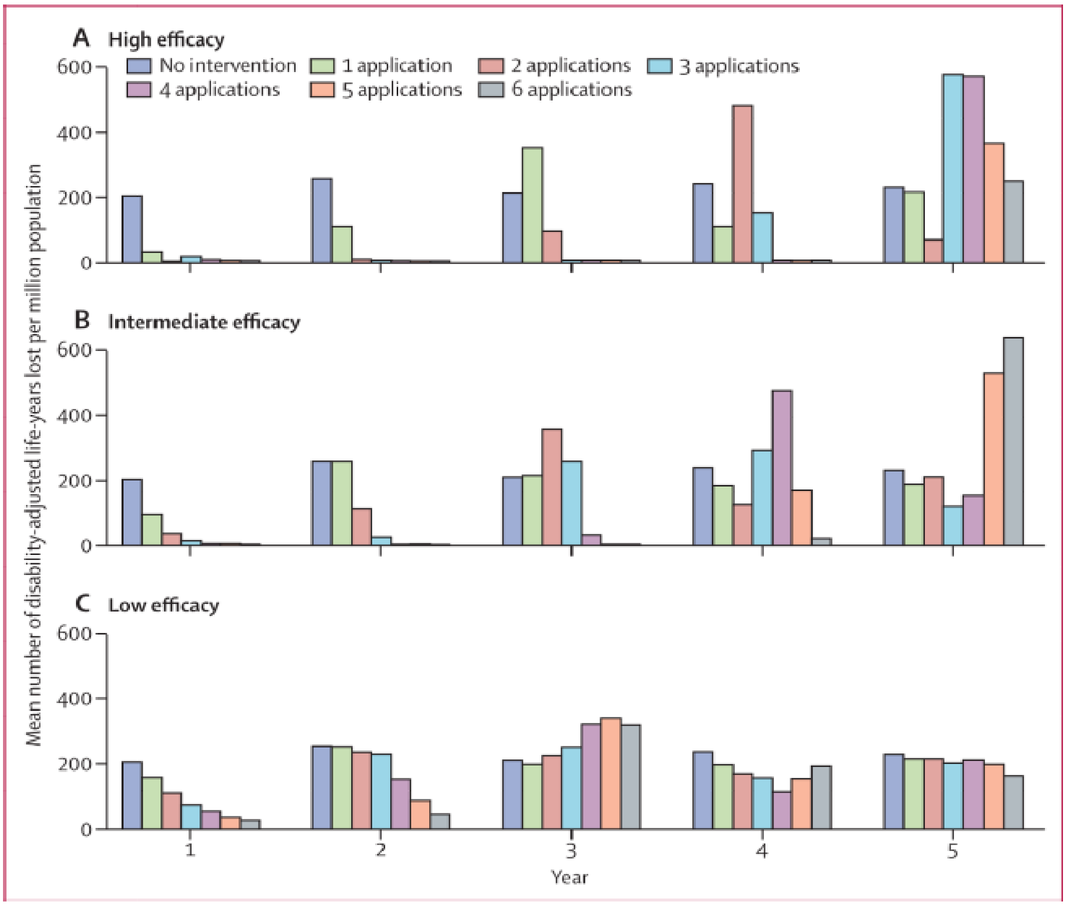

Figure 22: Effect of adult dengue vector control on dengue burden

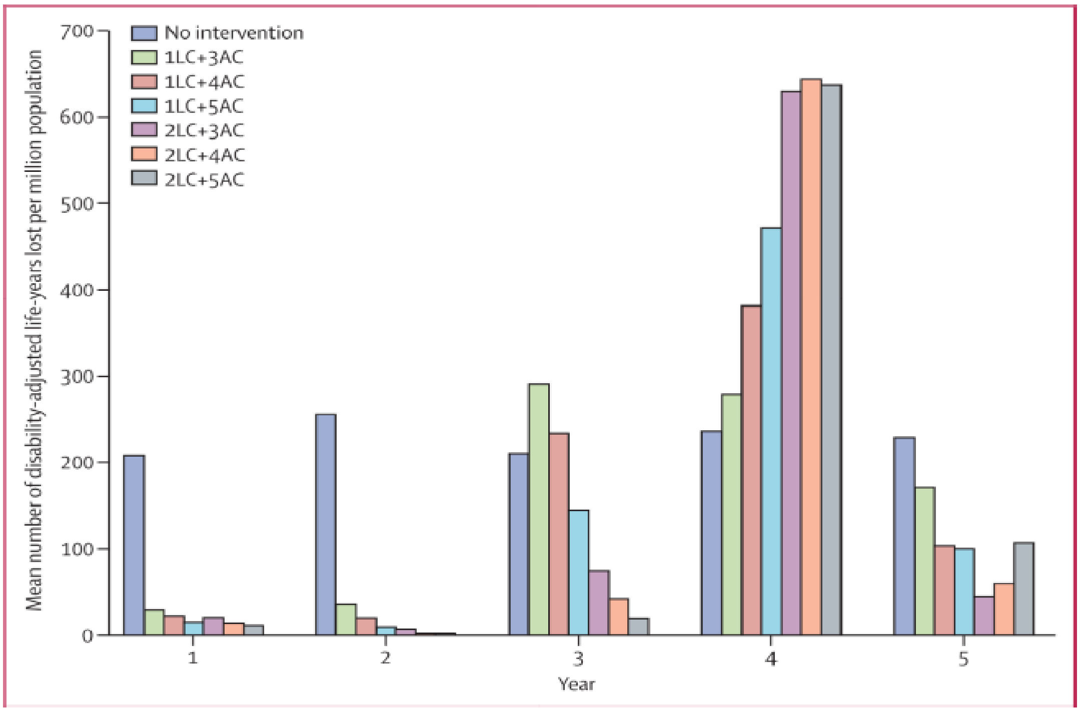

Figure 23: Effect of combined vector control on dengue burden
LC: Larval control, AC: adult control

All 43 interventions in the cost effectiveness plane was showed in Figure 23, which depicts the difference in costs and effectiveness between the strategies. Cost-effectiveness analysis showed that three strategies were non-dominated; no control, use of two applications of high-efficacy adult control, and use of six applications of high-efficacy adult control. (Figure 24)

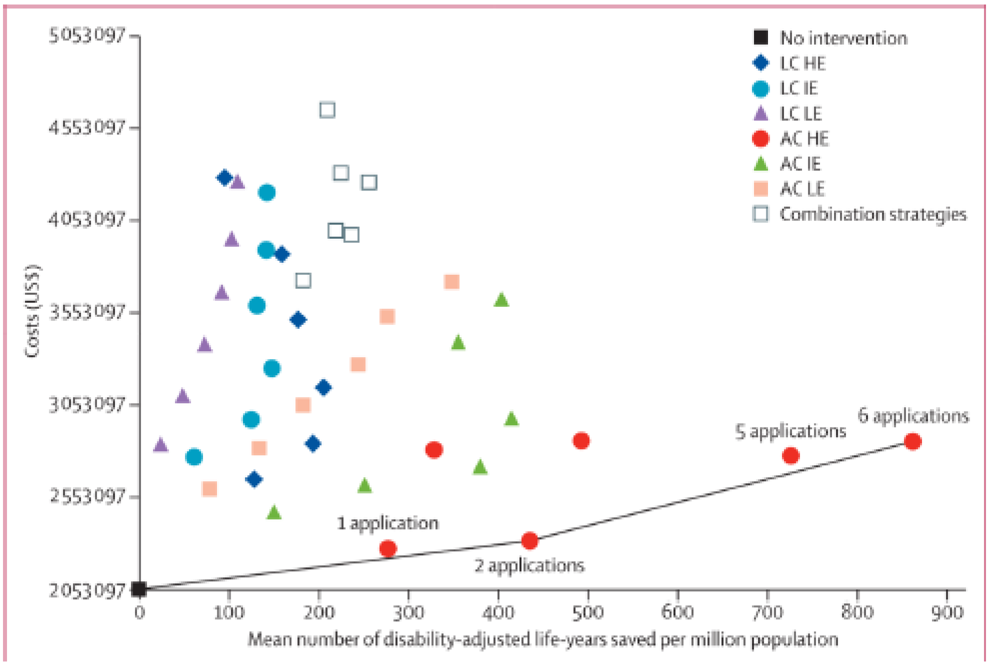

Figure 24: Cost effectiveness of different control strategies (the slopes of black lines represent the ICER of the non-dominated strategies)

The ICER for the strategy using two applications of high-efficacy adult control was $615 per DALY saved; whereas for the use of six applications of high-efficacy adult control was $1267 per DALY saved. (Table 20). Sensitivity analysis showed that if cost of adult control was more than 8.2 times the cost of larval control, then all strategies based on adult control became dominated.

Table 20: Estimated ICER for non-dominated strategies, Luz PM et al. (2011)

Intervention strategy	ICER
2 high-efficacy adult vector control applications per year	US$615 per DALY saved
6 high-efficacy adult vector control applications per year	US$1267 per DALY saved

The authors concluded that the economic assessment was done in the context of an urban area with endemic dengue, hence could be generalised to settings with endemic dengue. More studies of insecticide delivery, efficacy and effect are needed for the guidance of future economic analysis of vector control. Year-round larval control can be counterproductive, exacerbating epidemics in later years because of evolution of insecticide resistance and loss of herd immunity. Reassessment of vector control policies that are based on larval control only was suggested. [52]

Baly A et al. (2007) conducted a cost effectiveness analysis to present a cost-effectiveness of two alternative strategies for *Aedes aegypti* control: a vertical versus a community-based approach. An economic appraisal was conducted of two strategies for *Aedes aegypti* control; a vertical versus a community-based approach. The study site was Santiago de Cuba involving 470,000 population. The assessment was carried out from a number of different perspectives; the health system provider, the vertical programme, a community perspective, and the society. Time horizon was two years (2001-2002). Costs were calculated for the period 2000 to 2002 in three pilot areas of Santiago de Cuba where a community intervention was implemented, compared with three control areas with routine vertical programme activities. Reduction in *A. aegypti* foci was chosen as the measure of effectiveness. Economic costs of both strategies were estimated for year 2000 (before intervention), 2001 and 2002 (during implementation).

Community participation strategy consisted of forming community working group, volunteer participation with no financial incentives, members then indentify problem and needs, elaborate, implement and evaluate action plans, with necessary equipment and materials were provided free of charge by local government. Meanwhile, vertical vector control programme consisted of focal and perifocal larval control, blanket spraying, replacing defect water tank, reducing house inspection and training local leaders.

They found total cost (US$) of the vertical *Aedes aegypti* control programme in 2000 to 2002 was US$ 24,395,039 (US$ 52 per inhabitant). Economic cost comparing community participation strategy (intervention) and vertical vector control programme (control areas) in 2000 to 2002 is as illustrated below.

Table 21: Economic cost of community participation versus vertical control programme, Santiago de Cuba 2000-2002

Input	**Intervention (community participation)**		**Control (vertical vector control)**	
Recurrent cost (personnel, supplies, training and social communication, operating cost), capital cost & community cost	Baseline	Total (2001-2002)	Baseline	Total (2001-2002)
Total cost (US$)	243,746	692,290	263,486	825,309

In term of cost-effectiveness, the community-based approach was more cost-effective compared to control from health system perspective (US$964 versus US$ 1406 per focus) as well as from society perspective (US$1508 versus US$1767 per focus). (Table 22).

Table 22: Cost effectiveness ratios and incremental cost-effectiveness ratios for participatory and vertical *Aedes aegypti* control, Santiago de Cuba, 2001-2002

Perspective	Intervention area		Control area		Incremental cost per focus eliminated
	Total cost (US$, 2001-2002)	CER	Total cost (US$,2001-2002)	CER	
Health system	442,483	**964**	656,680	**1406**	26775
Society	692,291	**1508**	825,309	**1767**	-10147
Community	249,808	544	168,629	361	16628
Vertical programme	364,796	795	552,644	1183	23481

They concluded the described community based intervention for *A.aegypti* control when intertwined with the vertical control programme, appears to be the superior strategy. In Santiago de Cuba, the dengue control programme integrating a community based intervention strategy was more cost-effective than an intensive vertical programme alone. Although entomological indices reported are very low in Cuba, dengue outbreaks have occurred with this level of infestation. These finding could be useful for health decision making in allocating resources for vector control programme in other countries. [53]

Baly A et al. (2012) in another study conducted a cost analysis to assess the economic cost of routine *Aedes aegypti* control in at risk environment without dengue endemicity and the incremental costs incurred during a sporadic outbreak. The study was conducted in 2006, in Guantanamo, east Cuba. In this study, analysis was done from societal perspective. Cost incurred in 2006 in dengue control was calculated in months without dengue transmission (January-July) and during an outbreak (August-December) using micro costing method except for the hospital, where macro costing was used to derive the inpatient cost per day for the wards managing dengue cases. Costs were classified by actor/activity and subsequently as recurrent and capital costs. Recurrent cost were salaries, supplies and materials (insecticide, larvicide, diagnostic test, drugs, protective clothing, glove, office materials), operational cost (fuel & lubricants), vehicle rent, vehicle & building, food and per diem, maintenance of equipment), and utilities (electricity, water, telephone). Meanwhile, capital means included were portable fogging equipment, trucks for spatial spraying, laboratory equipment, furniture and their time of use. Data sources were bookkeeping records, registers, direct observations and semi-structured interviews with health system managers, and randomly selected nurses, family doctors and vector control personnel. All costs were analysed at constant prices and converted at the 2006 official exchange rate of 1peso equals to 0.92USD. The study involved approximately 244,100 Guantanamo inhabitants (68,648 households). The vector control programme consisted of entomological surveillance, source reduction through periodic inspection of houses, larviciding with temephos in water storage containers, selective perifocal insecticide spraying of adult mosquitoes, health education, and enforcement of legislation.

They found the total economic cost per inhabitant per months increased from USD2.76 in months without transmission to USD6.05 during an outbreak for dengue control and management. In absolute term, the average monthly cost increased from USD 673,959 (in month without transmission) to USD 1,477,617 (during an outbreak); amounted to 0.7% of the country's monthly GDP in period without transmission to 1.5% in the period with transmission.

The cost per inhabitant per month for *Aedes aegypti* vector conrol programme increased from USD1.67 to USD 1.88 per inhabitant per month, or USD 408,281.8 (in month without transmission) to USD 459 406.0 per month (during an outbreak). Incremental costs during the outbreak were mainly incurred by the population, the primary/secondary level of healthcare system, hardly by vector control programme (USD1.64, USD1.44 and USD0.21 per inhabitant per month respectively). In both periods, the main cost drivers for *Aedes* control programme, the healthcare system and the community were the value of personnel and volunteer time or productivity losses.They concluded intensive efforts to keep *A.aegypti* infestation low entail important economic costs for society. When a dengue outbreak does occur eventually, costs increase sharply. In-depth studies should assess which mix of activities and actors could maximize the effectiveness and cost-effectiveness of routine *Aedes* control and dengue prevention.[54]

In another cost analysis done in Malaysia, Packeriasamy PR et al.(2015) estimated the cost of the national dengue vector control programme in the country through examination of inputs and costs incurred by public agencies at all levels of the government. In this study, 20 study sites comprised of eight District Health Department (DHD), three State Health Departments, one Federal (Vector Borne Disease Control, Disease Control Division) and eight local authorities in the selected DHD participated, sampled using probability proportional to size method. Bottom-up costing approach was used. All elements of the vector control program were initially identified, following with resource utilisation and unit cost of each resource obtained. Information was collected to reflect resource used in 2010. Analysis was done from funder (government) perspective, only direct cost included. Data included capital and recurrent expenditures; annual discount rate of 3% was used for capital cost. Data from DHD recorded using nine line items (human resources, buildings, vehicles, fogging equipment, pesticides, PPE, outsourced services, National dengue prevention advertisement campaign) and five functional groups (inspection of premises, entomological surveillance, fogging, larviciding, and health education). Vector control activities at SHD and FHD used only three line items (human resource, building, vehicle with advertisement campaign). Estimates of vector control cost for the district, state and federal level were summed upto provide the estimated national dengue vector control cost for Malaysia in 2010. All costs are reported in US$ using the average 2010 exchange rate (US$1 equals to RM3.20).

The study involved 16,676 dengue cases from eight selected DHD (36.1% of 46,171 cases reported in Malaysia in 2010. Intervention was Dengue vector control (summarised in nine line items and five functional groups) (Table 23). The line items consisted of human resources, buildings, vehicles, fogging equipment, pesticides, PPE, outsourced services, National dengue prevention advertisement campaign and the five functional groups were inspection of premises, entomological surveillance, fogging, larviciding, health education.

Table 23: Description of line items and functional groups

Category	Description
Line items	
Human resources	Annual salaries and other allowances for staff such as overtime claims, housing & uniform allowances,wages for temporary workers hired during outbreak
Buildings	Buildings used for administration of programme, storage of equipment, inclusive of both capital (annual purchase price or annual rentals) and recurrent cost (eg insurance, utilities,maintenance)
Vehicles	Vehicles used in vector control activities such as fogging activities inclusive of both capital (annual purchase price or annual rentals) and recurrent cost (fuel, maintenance, insurance)
Fogging equipment	Fogging/larvicidng equipment, either ULV equipment mounted on pick-up trucks or thermal fogging machines carried on the back of vector control officers, inclusive of both capital (annual purchase price) and recurrent cost (fuel and maintenance)
Pesticides	Insecticides used for larvicing and fogging activities
PPE	PPE including goggles, mask, gloves, respirator, bootsused during larviciding and fogging activities
Outsourced services	Cost of fogging and larviciding activities subcontracted to private companies
* National dengue prevention advertisement programme	Cost of national broadcasting in radio, television, local newspapers, including hiring of celebrities to promote dengue prevention campaign
Functional group	
Inspection of premises	Inspection of building including houses, shops, construction sites, schools for breeding sites
Entomological surveillance	Activities to collect data for entomological indices, e.g. Aedes and Breteau Index
Fogging	Back mounted thermal fogging, truck-mounted thermal fogging at premises and areas found to have dengue cases
Larviciding	Application of insecticides at potential breeding sites of premises and areas found to have dengue cases
Health education	Activities to educate the community including distributing flyer, pamphlet, brochure, giving educational talk,banner and bunting, engaging local community leaders through COMBI programme to spearhead campaign to keep the living environment clean and mosquito free

COMBI: Communication for Behavioural Impact, PPE:Personal Protective Equipment, ULV: Ultra low volume
*This line item applies only at Federal Health Department

They found, Malaysia spent an estimated US$73.5 million (95%CI US$million 62.0, 86.3) for the national dengue vector control, constituting 0.03% of the country's GDP in 2010 (US$247.5billion) and 1.2% of the total government funding for healthcare in Malaysia (US$6.0billion). Approximately 92.2% of these costs was incurred at DHD level. Overall, 91.4% of the national costs for dengue vector control activities were for recurrent expenditures, mainly for salaries and allowances for healthcare personnel involved. Human resources costs made up 64.8% of total national vector control costs. The cost of pesticide amounted to 10.9% of the total cost. (Table 24).

Table 24: Dengue vector control cost by line item at different level, Malaysia (2010)

Item	District	State	Federal	All level
Aggregate (US$Million)				
Human resource	44.41 (38.43-50.92)	3.06 (2.11-3.98)	0.14	47.61 (42.55-55.03)
Building	3.87 (2.99-4.97)	0.65 (0.55-0.74)	0.04	4.56(3.78-5.76)
Vehicles	5.15 (4.17-6.42)	0.29 (0.25-0.35)	0.01	5.44(4.53-6.77)
Fogging equipment	3.89 (2.80-5.31)	NA	NA	3.89(2.80-5.31)
Pesticides	8.02 (5.97-10.57)	NA	NA	8.02 (5.97-10.57)
Personal Protective Equipment	1.83 (1.62-2.06)	NA	NA	1.83 (1.62-2.06)
Outsourced fogging services	0.57 (0.00-1.29)	NA	NA	0.57 (0.00-1.29)
National dengue advertisement programme	NA	NA	NA	1.53
Total dengue vector control costs(US$Mil)	67.73 (57.20, 79.85)	4.00 (3.11, 4.78)	1.72	73.45 (62-86)
Per reported case (US$)	1,467.0 (1239,1729)	86.6 (67.31,103.54)	37.21	1590.9 (1343-1870)

Per capita population (US$)	2.47 (2.09, 2.91)	0.15 (0.11, 0.17)	0.06	2.68 (2.26-3.15)

NA:not applicable

The average district vector control cost was US$1.4 million, ranged from US$0.2million in Sik to US$2.8 million in Gombak. A linear regression confirmed that DHD with more annual reported dengue cases tended to have more costly vector control expenditures. The regression equation calculated was;
DHD cost (US$) = $622,000 + cases x $380 ($R^2$=0.790, p=0.019)

The average cost per reported case at the district level was US$1,467.The main drivers for cost in the DHD were for human resources (60.7%), and pesticides (13.6%). Pesticides used for fogging and larviciding activities were in the form of liquid based (average use per district was 6,774 litre) and powder based pesticides (average use per district was 590kg).Meanwhile, the average cost for State Vector Control cost was US$0.3million, ranging from US$0.2million (Malacca) to US$0.3million (Kedah). At the federal level, the estimated vector control costs come to US$1.7million. The main driver for cost in SHD/FHD was for human resources.

The authors concluded that Malaysia is an upper middle income country that spends annually approximately 5% of total GDP on health overall, and 0.03% specifically on dengue vector control. Dengue poses significant economic burden to the country with a combined **annual cost of prevention and illness of US$175.7million.** Malaysia has been reliant on a government funded integrated vector control programme which include effort to garner community support through health education activities. Innovative control technologies against this disease include the Toxorhynchites larvae (a biological control method), genetically sterile mosquitoes, *Wolbachia* inserted into mosquitoes and the dengue vaccine. This study's quantification of dengue economic burden informs policy makers and stakeholders regarding the implementation of existing and new technologies for controlling dengue. [55]

Kay BH et al. (2010) in the cross sectional and cost analysis conducted involving 46 communes in northern and central Vietnam (Northern = 62,563 population, central=11,110 population) found the program cost were as follows**;**

- The recurrent annual cost at Northern - NPC was VND 40 million (6,134 international dollars) with an additional 10% used for start-up costs incurred in the first year.
- Per person, the recurrent annual project costs ranged from 0.28 international dollars at Central (CPC) to 0.61 international dollars per person (in NPC) and 0.89 international dollars per person (in NEC).[49]

Caprara A et al. (2015) in the cluster randomised controlled trial to implement a novel intervention strategy in Brazil using an ecohealth approach also estimated cost for the approach. The study involved ten intervention and ten control clusters. Intervention consisted of a)Community workshop to organize social mobilization by National Health Service professionals, educators and Endemic Disease Agents (EDA), b)involvement of community during clean-up campaign, c)mobilising school children and elderly regarding dengue prevention, and d)distribution of information, education and communication (IEC) materials.

They found the total costs of intervention were US$18.89/house and costs related to ecohealth intervention were US$2.23/house. The distribution of cost for the intervention in household showed that staff cost was valued at US$185/ month (11 Endemic Disease Agents) and US$277/month (one field coordinator), which was the most important component accounting for 85.8% of total costs. They concluded the difference regarding the cost of the intervention were reasonable and could be adopted by public health services. [45]

6.4.1 FINANCIAL IMPLICATION

A number of published researches have attempted to estimate the cost-related and economic burden of dengue illness as dengue is endemic in Malaysia. There were three comprehensive researches conducted in Malaysia to estimate the cost of dengue vector control activities and cost of dengue in Malaysia between the year 2005 to 2010.[14,46-50] According to Shepard et al., the annual economic burden of dengue in the year 2009 was approximately MYR359.79 million from a societal perspective which include both public and private healthcare facilities in Malaysia. [47]

Prevention of dengue in Malaysia was established many years ago using the IVM approach. The vector control approaches include chemical, environmental and community participation. This programme was led by the Ministry of Health with collaboration with other government agencies from states and districts all over the country. Based on the research, the high expenditure of vector control activities were primarily related to the human resources and pesticides.[14]Costs such as equipment, facilities, health education and advertisement campaign contributed to a small fraction of the expenditure. Therefore the aim of this analysis was to estimate the current economic implication of integrated vector control activities in Malaysia.

The cost data were extracted from a published study of eight Malaysia's DHD and local authorities on dengue vector control.[14] The eight selected study sites reported to four different SHD to represent the load of reported dengue cases and intensity of dengue vector control activities. Detail of resources and costs use at the district level was reported as line item and functional groups as Table 25. The costs were adjusted accordingly until the year 2018.

Table 25: Description of resources and costs[14,46]

Category	Description
Line items	
Human resources	Annual salaries, allowances
Buildings	Annualized purchase/recurrent costs
Vehicles	Annualized purchase/recurrent costs
Fogging equipment	Annualized purchase/recurrent costs
Pesticides	Use for larvaciding and fogging activities
PPE	Use for larvaciding and fogging activities
Outsourced services	Fogging and larvaciding activities subcontracted to private companies
National dengue prevention advertisement	Broadcasting in radio, television and local newspaper
Functional group	

Inspection of premises	Buildings (for mosquito breeding sites)
Entomological surveillance	Entomological indices
Fogging	Back-mounted thermal fogging and truck mounted ULV fogging
Larvaciding	Application of insecticides at potential breeding sites
Health education	Activity to educate the community including COMBI

COMBI = Communication for behavioural impact

A decreasing trend in the statistic of dengue cases and mortality were observed in Malaysia from the year 2015 onwards (Figure 25 and 26). An estimated expansion factor was applied for the data from 2010 until 2014 to estimate the true number of dengue cases. However, since the introduction of the dengue rapid test kit in 2014, the number of cases reported has increased significantly. Hence, no expansion factor was applied to the data from 2014 onwards. The number of dengue cases from 2013 was also compared against the projected number of cases using the expansion factor to validate the number of reported cases from 2014 onwards. Proportion of inpatient was estimated based on the available published literature on proportion of ambulatory dengue cases (58%). This information was cross-validated with the discharge summary of dengue cases within Ministry of Health in the year 2018.

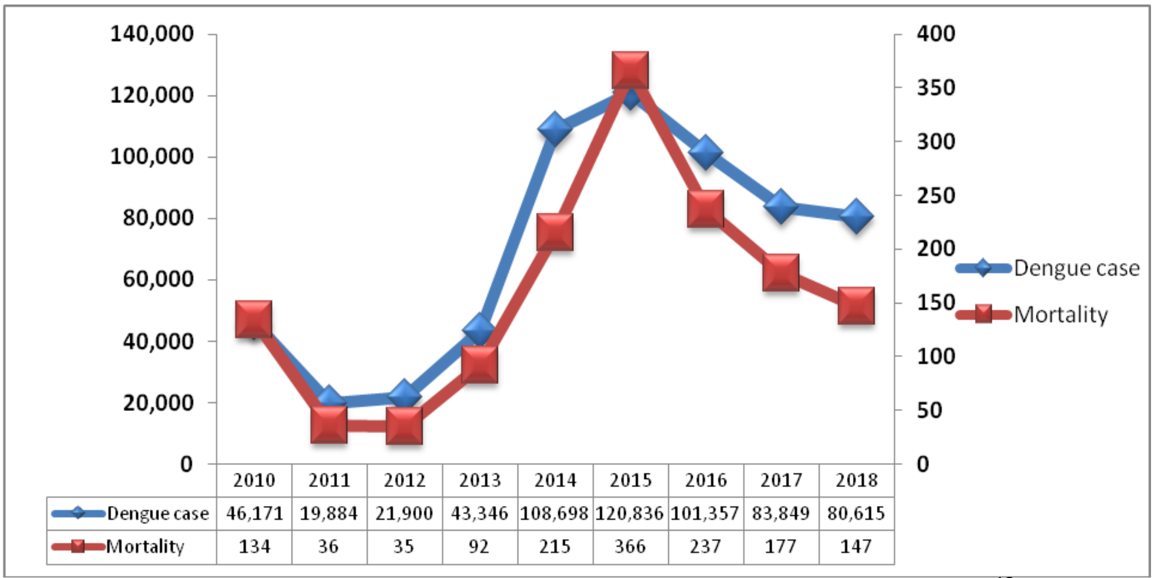

Figure 25: Dengue case and mortality by year in Malaysia [49]

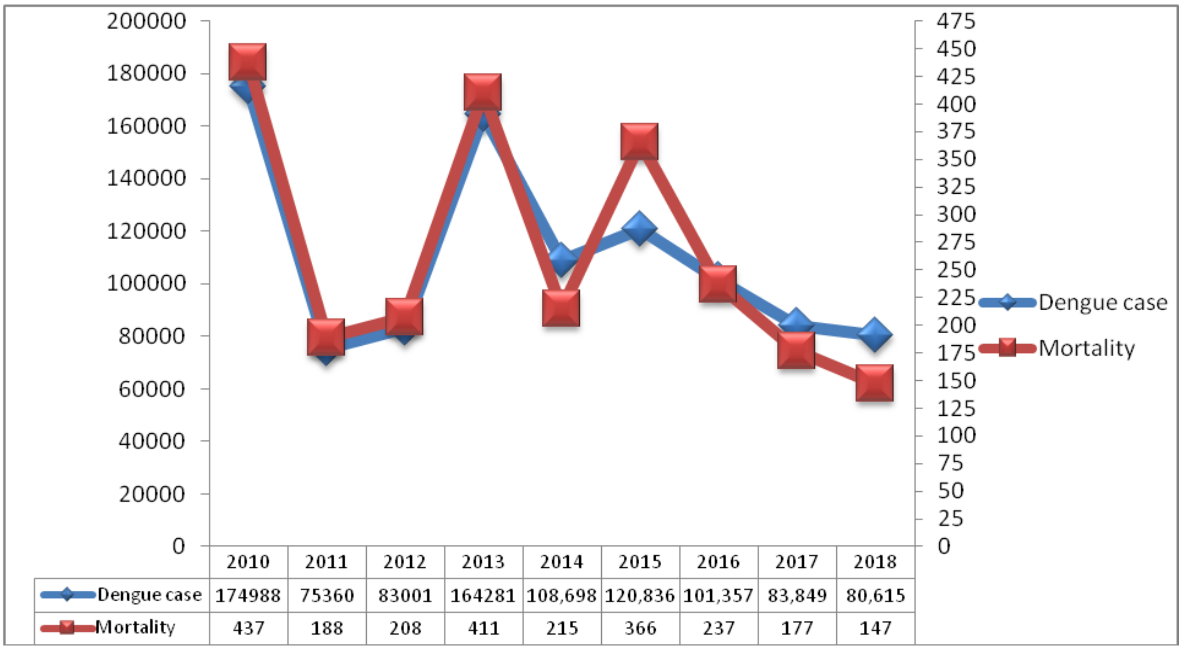

Figure 26: Malaysian dengue statistic (case and mortality) with expansion factor [47,49]

(Expansion factor = 3.79)

Summary of the costs data from local published literatures and available local data resources were illustrated as in Table 26.

Table 26: Cost related to dengue control and management

Parameter	Value	Source
Estimated cost per hospitalisation (2009)*	MYR 2,788	Shepard DS.et al 2012
Estimated cost per ambulatory visit (2009)*	MYR 1,624	Shepard DS.et al 2012
Annual cost		
Entomological surveillance	MYR 20,176,338	Packieriasamy PR. et al 2015
Inspection of premises	MYR 65,386,280	
Fogging	MYR 83,320,802	
Larvaciding	MYR 48,572,665	
Health education	MYR 35,495,409	
National dengue prevention advertisement campaign	MYR 5,716,629	
Outsource Private (Selangor, KL Johor) with existing services	MYR 2,129,724	

*based on societal perspective

Several limitations however, were acknowledged in the analysis. This analysis was conducted based on the retrievable cost data which reflected the common approaches within the integrated dengue vector control in Malaysia. No addition of other approaches such as biological intervention was considered in this analysis. The cost of the IVM approach were considered to be constant and subjected to the information in the published research.[14,46] Updated data collection on cost was not possible due to the limitation of the timeframe and resources needed. Cost of dengue rapid test kit was not included as it is now used as a tool for dengue detection in both public and private healthcare facilities in Malaysia. Analysis was done for year 2016 to 2018 only.

The analysis demonstrated there was reduction in the number of dengue cases both ambulatory and hospitalised patients throughout 2016 to 2018, reflecting estimated total cost saving from the reduction of dengue cases. The total cost of integrated dengue vector control activities since 2016 to 2018 was approximately MYR 772 million. Meanwhile, the total cost from reduction of dengue cases using societal perspective over the same period was estimated as MYR 101 million. There was a substantial difference between the prevention control expenditure and the monetary benefit. However, the annual estimated economic burden were subjected to the number of dengue cases throughout the years.

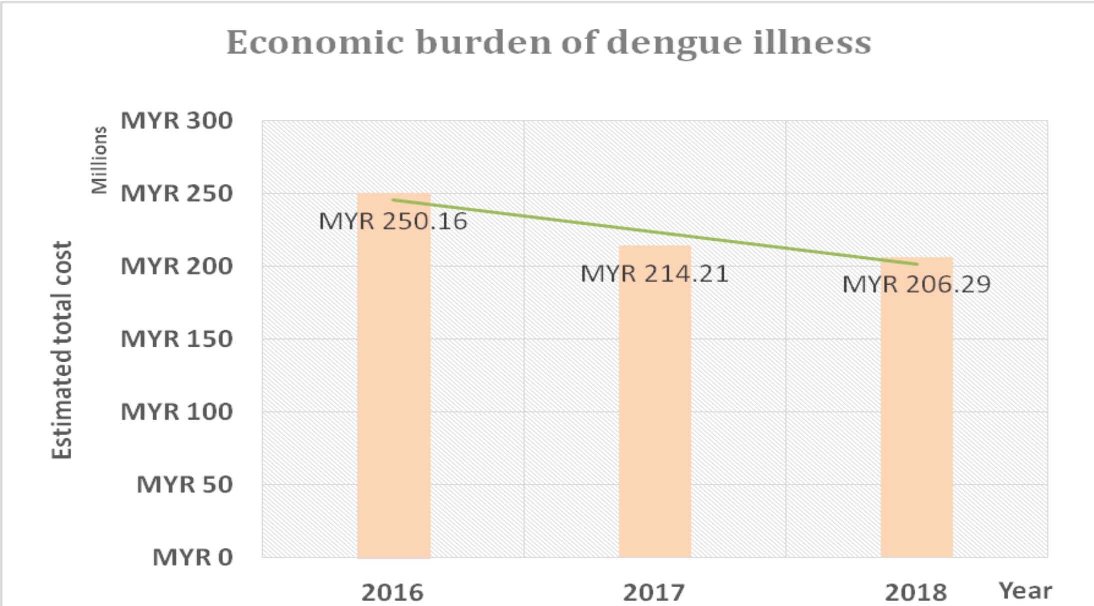

Figure 27: Estimated economic burden of dengue illness (2016-2018)

Over three years (2016 to 2018), the proportion of total cost saving from reduction of dengue cases (MYR 101million) relative to total cost of integrated dengue vector control (MYR 772 million) was approximately 13.08%. There was also minimal reduction (15.07%) in cost-related to dengue illness (MYR 101 million) relative to the estimated annual economic burden of dengue illness demonstrated over three years (MYR 670 million). Summary of the results are illustrated as in Table 27.

Table 27: Total costs of dengue management in Malaysia

Total cost	Value
Total reduction of hospitalised dengue cases (2016-2018)	**16,893**
Total reduction of ambulatory dengue cases (2016-2018)	**23,328**
Total cost of dengue vector control activities (2016-2018)	**MYR 772,702,458**
Total cost saving (reduction in dengue cases, 2016-2018)	**MYR 101,079,949**
Estimated economic burden (2016-2018)	**MYR 670,660,897**

This analysis gives useful information on the current effectiveness of dengue vector control in monetary dimension and the potential challenges that need to be addressed to further improve the dengue control in Malaysia. New strategy to strengthen the dengue vector control activities such as the use of *Wolbachia spp* in controlling mosquito population by the Ministry of Health were hoped to further improve the current status of dengue epidemic in Malaysia.

Based on the estimated cost saving relative to the expenditure of the IVM activities in Malaysia, further evaluation, reinforcement and improvement of the existing activities could probably lead to higher cost saving to the country in the longer term. The programme achievement would potentially be beneficial to other countries with similar epidemic status especially within this region.

As of 8th May 2019, the total dengue cases reported was 45,660. Therefore, estimated total cost of dengue illness is MYR 116 million (May 2019), and MYR 348 million (December 2019), with the cost of vector control in 2019 estimated to remain as in 2018 (MYR 260 million).

6.5 SOCIAL

There were two retrieavable evidence on the social aspect of IVM for *Aedes* control, which comprised of pre-post intervention studies.

- **Acceptance**

Kittayapong et al. (2012) in the cRCT described above involved 441 household (intervention cluster) and 448 household (control cluster) in urban and peri-urban settings in Chachoengsao province, eastern Thailand. They aimed to demonstrate an application of integrated, community-based, eco-bio-social strategies in combination with locally-produced eco-friendly vector control tools in the dengue control programme.

Intervention carried out for six-months were eco-bio-social or ecohealth strategies which comprised of; 1)ecosystem management (garbage and environmental management, provision of piped supply, public land space maintenance), 2) source reduction and social mobilisation (removal/reduction of water containers, protection of water containers), and 3)integrated physical and biological methods (applying tight screen covers or lids (MosNet),Mosquito Traps (Mos House®) and portable vacuum aspirator (MosCatch™). and applying biocontrol agent, *Mesocyclops thermocyclopoides* (copepods) or biolarvicide, *Bacillus thuringiensis* subsp. *israelensis (Bti sacs)).* Data on acceptance of the vector control measures was collected using a structured questionnaire.

They found a higher percentage of people in the treatment clusters compared to the control clusters (67.1% versus 52.1%, p=0.006) agreed that applying copepods and Bti to water-holding containers was not complicated. The percentage of people in the treatment clusters who agreed that it was only health volunteers who were responsible for dengue prevention in the community was significantly lower than in the control clusters (12.9% versus 26.1%, p=0.013). [52 level II-1]

Meanwhile, Wai KT et al.(2012) in the study conducted in Myanmar found at the end of the intervention period, nearly 45% of cluster dwellers accepted pyriproxyfen alone or in combination with other measures (Table 28). They perceived the chemical as being extremely beneficial and nearly 60% had full confidence in it. Of cluster dwellers using *Bti* for their ceramic bowls, only 28% perceived it to be extremely beneficial. Lid covers were accepted by 52 households per cluster and 60% of cluster dwellers were fully confident to use them continuously which was important for vector control in the intervention clusters. Dragon fly nymphs were found in 12 households per cluster but nearly 60% of cluster dwellers found those nymphs as being extremely beneficial and perceived them as being important in removal of larvae and pupae from their water containers. Nearly 42% of cluster dwellers perceived waste collection bags as extremely beneficial for them and 52% was fully confident for continuity in use. There were no differences between high and low risk clusters. The results indicated that people were less enthusiastic about *Bti* and cotton net sweepers.

In the focus group discussion (FGD) and observations following the intervention, it became clear that householders' responsibility in managing dengue vector breeding sites was enhanced. They became interested in the inspection and removal of larvae in their homes; they used lid covers and cotton net sweepers and scrubbed the containers and changed the water regularly in contrast to responses at baseline when household members did not regularly scrubbing and changing water especially of the large containers. [54 level II-2]

Table 28: Acceptability of six intervention tools in intervention clusters

Level of cluster dwellers acceptance by intervention	Average number of clusters	Proportion of acceptance (%)
Pyroxifen		
Very desirable/extremely beneficial	5.17	44.6
Definitely feasible in household	5.17	43.9
Very important	4.67	39.4
Confident	72	59.3
Bti		
Very desirable/extremely beneficial	6	28.0
Definitely feasible in household	6	32.5
Very important	6	28.2
Confident	10	49.2
Lid covers		
Very desirable/extremely beneficial	27	51.6
Definitely feasible in household	26	50.5
Very important	24	46.1
Confident	31	60.5
Cotton-net sweepers		
Very desirable/extremely beneficial	15	32.7
Definitely feasible in household	14	31.2
Very important	14	30.3
Confident	14	30.3
Dragon fly nymphs		
Very desirable/extremely beneficial	7	57.4
Definitely feasible in household	7	59.4
Very important	7	58.0
Confident	8	64.3
Waste collection bags		
Very desirable/extremely beneficial	31	41.9
Definitely feasible in household	29	38.1
Very important	31	41.5
Confident	39	53.0

- **Knowledge, attitude and practice (KAP)**

Kay BH et al. (2010) in the study described above found in Northern Vietnam, KAP was higher in NPC and NEC compared to NCC with respect to the importance of collecting discarded item and inoculating Mesocyclops. While, in central Vietnam, general knowledge of dengue was higher at CPC than CCC ($\chi 2 = 12.82$; $p < 0.001$). In terms of dengue vector-control practices in the communes, the proportion of householders who reported cleaning water containers and removing discarded containers as larval control methods did not differ significantly in CPC 4.5 years after project completion ($\chi 2 = 0.004$; $p = 0.95$), but there was a significant reduction in the proportion of participants that continued to introduce *Mesocyclops* (78.5% versus 21.2%). [54 level II-2]

Tana et al. (2012) conducted pre and post intervention study to build an innovative community-centered dengue-ecosystem management intervention in the city and to assess the process and results in Indonesia. In this study, entomological surveys and household surveys were carried out in six randomly selected neighborhoods in Yogyakarta city, as baseline, documents were analysed and different stakeholders involved in dengue control and environmental management were interviewed. Then a community-centered dengue-ecosystem management intervention was built up in two of the neighborhoods (Demangan and Giwangan) whereas two neighborhoods served as controls with no intervention (Tahunan and Bener). Intervention consisted of community involvement and empowerment (meetings, forum, leaders etc), involvement of other partner (environmental health forum, local political authorities etc) and production of intervention tools such as communication materials and development of awareness campaign in school.Six months after the intervention, follow up surveys (household interviews and entomological) were conducted as well as focus group discussions and key informant interviews.

They found at baseline, there was a lack of community involvement and knowledge in dengue control. The community sees dengue control as government responsibility, and has limited knowledge about mosquito breeding places.Six months after the start of the intervention phase, they reported the entire program (planning, implementation and evaluation) was led by the community with the involvement of women groups. Post-intervention surveys in the study neighbourhoods showed that respondents were more knowledgeable about dengue and dengue prevention, than respondents in the control group, respondents expressing the need for water container management and other vector control measures increased substantially. (Table 29).

The intervention resulted in better community knowledge, attitude and practices in dengue prevention, increased household and community participation, improved partnership including a variety of stakeholders with prospects for sustainability, vector control efforts refocused on environmental and health issues, increased community ownership on dengue vector management including broader community development activities such as solid waste management and recycling.
They concluded the community-centred approach needs a lot of effort at the beginning but has better prospects for sustainability than the vertical “top-down” approach. [60 level II-2]

Table 29: Knowledge about dengue prevention before and after

	Before		After		
Suggested actions	Control N=210	Intervention N=213	Control N= 200	Intervention N=201	Difference of difference
Do water container management at home	31.90%	35.01%	27.75%	71.40%	40.54%
Put larvivorous fish into water tanks	4.50%	7.20%	5%	51.70%	44.00%
Put mosquito wire screens on windows and doors	0.50%	2.70%	0.50%	45.80%	43.10%
Put pyriproxifen into the water	26%	28.30%	5.50%	41.30%	33.50%
Spray insecticide in your home	7.50%	6.70%	3%	10.40%	8.20%

Wai KT et al. (2012) in the study to analyse the feasibility and effectiveness of a partnership-driven ecosystem management intervention in reducing dengue vector breeding and constructing sustainable partnerships among multiple stakeholders in Myanmar, found at baseline, the overall knowledge of 2,000 respondents on dengue related issues was high but their container management practices were inadequate especially for productive large size containers. Qualitative evaluations after the intervention captured that people`s awareness of appropriate vector control options for specific containers was highly improved as well as positive attitudes towards joint actions. [59 level II-2]

- **Social participation, commitment and leadership**

Caprara et al. (2015) in a clusterRCT conducted in Brazil aimed at implementing a novel intervention strategy in Brazil using an ecohealth approach, and analysing its effectiveness and costs in reducing *Aedes aegypti* vector density as well as its acceptance, feasibility and sustainability. In the study, interventions were consisted of a) Community workshop to empower the community and have a collective responsibility for dengue prevention b) Involvement of community during clean-up campaign c) Mobilizing school children and elderly regarding dengue prevention d) Distribution of information, education and communication (IEC) materials; compared to routine vector control. During the intervention period, the process of empowerment-collaboration-mobilization by means of these indicators of community participation by Draper K.(leadership, planning and management, involvement of women, external support and monitoring and evaluation) were analysed. Social and anthropological field research (key informant interviews and participatory observations) derived qualitative data about social participation and community empowerment in the intervention clusters. The level of social participation was analysed by constructing spidergram.

They found differences in terms of social participation, commitment and leadership capacity in the ten clusters studied.(Figure 28). Some clusters (3 and 9)managed to organise the garbage collection with their respective Regional Secretariats and communities, while others (such as 6 and 5) were more passive and achieved only minimal collaboration. Community leadership was weak or almost non-existent in cluster 6. At the end of the study, a community member said that the collaborative action was a success (cluster 3). Among the frequent comment was;
I thought it was magnificent. It was organized as a social action, but it's always a big challenge. We can't always do this activity, but we know that there are many yards with buckets, bottles and other types of trash. It's a big challenge, because if

you don't do it today and don't do it again its complicated. But the idea remains of looking at the yard and recognizing breeding grounds for the vector (cluster 3).

The comment illustrates that cleaning backyard as a social event results not only to the elimination of breeding sites of the vector, but also as a form of creating awareness and motivation for the continuing care of the yard. They emphasised with the intervention, community participation was strengthened and elderly people and schools planned continuous actions together with the municipal workers.[45 level II-2]

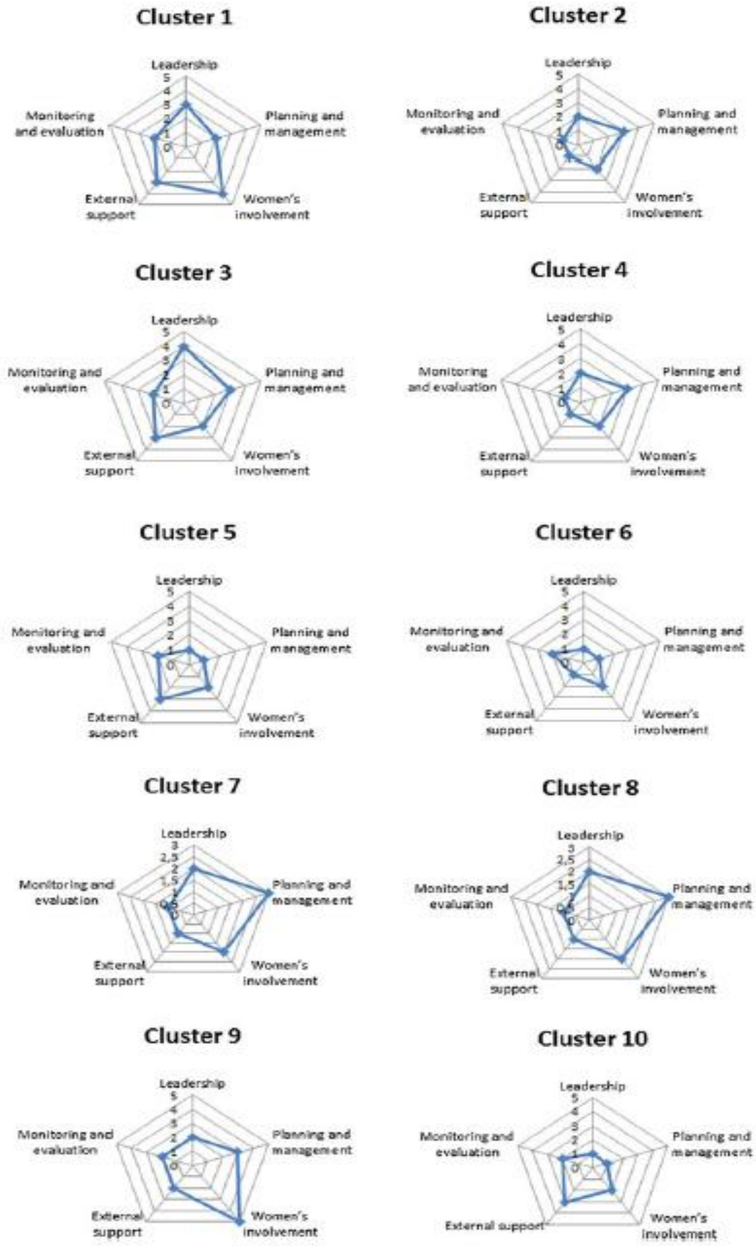

Figure 28: Spidergram assessing community participation

Tana et al. (2012) in their study reported that the intervention increased the percentage of families who participated in different community actions for dengue prevention. Intervention applied was community involvement and empowerment (meetings, forum, leaders etc), involvement of other partner (environmental health forum, local political authorities etc) and production of intervention tools such as communication materials and development of awareness campaign in school. Most frequently, cleaning up the environment, participating in meetings to discuss dengue, and checking water containers in houses and public spaces were mentioned. The percentage of families who were protecting or destroying breeding places increased in the intervention group (difference of differences of 6.3%). [60 level II-2]

Wai KT et al. (2012) conducted pre and post intervention study to build up and analyse the feasibility, process, and effectiveness of a partnership-driven ecosystem management intervention in reducing dengue vector breeding and constructing sustainable partnerships among multiple stakeholders in Myanmar. A community-based intervention study was conducted from May 2009 to January 2010 in Yangon city. Six high-risk and six low-risk clusters were randomised and allocated as intervention and routine service areas, respectively. For each cluster, 100 households were covered. Bi-monthly entomological evaluations (i.e. larval and pupal surveys) and household acceptability surveys in the six intervention clusters at the end of 6-month intervention period were conducted, supplemented by qualitative evaluations (focus group discussion and in-depth interviews). Intervention given was eco-friendly multi-stakeholder partner groups (Thingaha) trained for information dissemination and managing vector control tools with ward-based volunteers, informed decision-making of householders, followed by integrated vector management approach. Four Integrated vector management intervention tools were applied according to type of container and people preferences. Pyriproxyfen sand granules and *Bacillus ThuringiensisIsraelensis* (Bti) as chemical control, lid covers and cotton net sweepers as mechanical control, dragon fly nymphs as biological control and waste collection bags for water retaining discarded small containers in households were used for environmental management. In the control clusters, only routine control measures were carried out.

At baseline, there was little collaboration and partnership among stakeholders in dengue vector control and the community was a passive recipient of public health interventions. They found the intervention package mainly delivered by Eco-health friendly partner group (EFG) improved the understanding and shared responsibility among local authorities and the community. Distributing pamphlets and booklets and assisting people in the application of targeted container interventions strengthened the leadership of EFG and the development of sense of ownership by community members. [59 level II-2]

- **Preference**

Wai KT et al. (2012) in the study conducted in Myanmar to analyse the feasibility and effectiveness of a partnership-driven ecosystem management intervention in reducing dengue vector breeding and constructing sustainable partnerships among multiple stakeholders, found combined measures (chemical, mechanical and biological) were the most frequently favored (44.8% of cluster dwellers), while chemical measures (pyryproxyfen and Bti) were the second choice (34.2% of cluster dwellers) and mechanical measures (lid covers and cotton net sweepers) the third choice (16.5% of cluster dwellers). Biological measures (dragonfly nymphs) were preferred in a combined package but rarely alone.[59 level II-2]

6.6 ORGANIZATIONAL

Effective, long-term vector control and disease elimination calls for strong, well-funded national control programmes, comprehensive national and regional strategies, supported by close collaboration among partners in the global public health community. Sustainable programmes require technical guidelines that set out clear standard operating procedures, and are well managed with efficient logistics, monitoring and evaluation.[26]

Capacity building, in particular human resource development is a major challenge, because the IVM strategy requires skilled staff and adequate infrastructure at central and local levels. Core functions and essential competency required for IVM at central and local levels required are outlined in the core structure for training curricula on integrated vector management and the associated training materials. IVM must be actively advocated and communicated, and regular feedback is required on performance and impact to ensure continued support. The general public must be made aware of the strategy and participate in its implementation. Communications for reaching them should lead to behavioural change and empowerment.[28] To foster sustainability, interventions must focus on capacity building in the recipient community. In top down programs, the capacity for sustainability requires both organizational capability and people's expertise. Though it is challenging to involve the population in the control efforts, any measure adopted should be based more on community involvement than on vertical approaches. Institutionalization is a key process on the path toward sustainability. [61]

Health services must have personnel who are able to interact effectively with residents, and have role as health promoters and evaluators, while undertaking entomological surveillance and vector control. These personnel should be part of epidemiological surveillance teams and the actions that they recommend or take should be based on situational analysis. Training is needed to provide the field health personnel with good communication skills. Changing the nature of house visits by emphasizing communication and interpersonal communication may transmit more appropriate messages for behaviour modification. Adequate tools and materials for the personnel should be provided to respond to the objective.[62]

Strategic partnership for dengue prevention and control is identified as important source for vector control programme support. These partnerships can promote and sustain the coordination of actions among the administrator, government, health sector, education, economic, social as well as other sectors, volunteers and non governmental organisation, local authorities, industries and media. IVM is based on the foundation that effective control requires collaboration of various public and private agencies and community participation since community engagement is a key factor in assuring sustainability. [62]

According to the WHO Health and Environmental linkage, IVM strategies are designed to achieve the greatest disease control benefit in the most cost-effective manner, while minimising negative impacts on ecosystems (such as depletion of biodiversity) and adverse side effects on public health from the excessive use of chemicals in vector control. Rather than relying on single strategy, IVM stresses on the importance of understanding the local vector ecology and local patterns of disease transmission, and then choosing the appropriate vector control tools, from the range of options available. IVM requires a multi-sectoral approach to vector-borne disease control. For instance, Health Impact Assessment of new infrastructure development, e.g.water resource, irrigation and agriculture, can help identify potential impacts on vector-borne disease upstream of major policy decisions so effective action may be taken. IVM is not a panacea. However, in many settings, the use of IVM strategies has yielded sustainable reduction in disease and transmission rates.[63]

IVM involves public authorities at all levels, and should be included in national and regional directives and guidelines. IVM must be adjusted to the behaviour and properties of the target mosquito species. A number of methods available for mosquito control including physical, biological, environmental and chemical methods. Each method has its strength and weakness. Within the context of IVM, the selection and timing of a method or combination of methods should be based on surveillance data and evidence on cost-effectiveness intervention in achieving the expected outcomes. IVM requires long-term consistency and commitment.[64]

6.7 ETHICAL

Genetically engineered vectors, such as the GEOX513A *Aedes aegypti* have been designed to suppress their wild type population so as to reduce the transmission of vector-borne diseases in humans. The GEOX513A *Aedes aegypti* has been subject to a germline modification that includes a lethality gene. Specifically, a synthetic genetic sequence encoding a tetracycline repressible transcriptional activator (tVAT) is introduced into the mosquito with the intent of treating tetracycline dependency in the insect. In the absence of tetracycline, tVAT is expressed and this leads to death of most of mosquitoes carrying the trait. If tetracycline is present, then tVAT is repressed and the larvae can develop and reach adulthood. Female mosquitoes are the biters that spread the disease, so only the male GE mosquitoes are intended for release in the target area. Initially the Oxitec GE mosquitoes had been classified under US Food and Drug Administraion (FDA) as pharmaceutical product; however in 2017 it was regulated as pesticide under the US Environmental Protection Agency.[65]

However, the approach to genetically modified (GM) vectors for disease control raises few intrinsic ethical issues. Important environmental and human health concerns need to be assessed before release of any genetically modified organism. Each country needs to decide its own policy guidance for ethical genetic engineering of microorganisms, plants, animals and ecosystem, and to negotiate with neighbouring countries, this policy advice should be the product of open dialogue involving all sectors of the society. Part of the process is for society to set values for consensus on risk assessment. A universal minimal standard of risk assessment applicable to disease vectors need to be defined, as diseases cross national and international borders. These are the recommended components to be addressed in the guidance:-

- Before field release of transgenic insect, researches must assess all scientific and social issues associated with GM vectors and develop safety precautions to address potential risks
- The scientific and social risk should be minimized through careful design of the vector system, relevant laboratory experience and careful choice of site considering appropriate social and cultural factors
- A procedure for evaluationshould be set up even if there are not perceived to be any realistic risks
- There should be prior environmental, medical and social studies for site selection, and most appropriate site chosen basing from these data
- Information should be exchanged as broadly as possible with community leaders, members of local community and mass media

One of the main concerns of releasing GM organisms is environmental risk. There are concerns over unknown long term effect in human and the ecosystem.Because no human action has 0% risk, the principles of both benefits and risk are used to assess this technology and are central to any public health programme. The basic ethical principle of autonomy, justice, beneficence and non-maleficence can be applied to help decision making in the phase of bioethical dilemma.

Because of limited resources and experiences, there is a need for policy guidance for genetic engineering of vectors in each country before any release of GMOs. While there is dilemma to combat infectious disease using genomics and biotechnology as opposed to implementing existing practical measures to curb the vectors, the former approach would possibly be one of the strategy in the future. [66]

6.8 LEGAL

Uniform legislation across the WHO European Region (53 nations) on the use of mosquito control agents is a highly desirable goal. Within the European Union, legislation is implemented through the Biocidal Product Directive (BPD)(98/8/EG) and the Biocidal Product Regulation (EU) No 528/2012. The list of authorized biocides will undergo changes over the years.[64]

In Malaysia, legislations to cover the prevention and control of vector-borne diseases are; 1) Destruction of Disease-Bearing Insect Act (DDBIA) 1975 (Act 154), 2) Prevention and Control of Infectious Disease Act 1988 (Act 342), and 3) Local Government Act 1976 (Act 171). The DDBIA 1975 was enforced throughout the country effective from 23 August 1982. The Destruction of Disease-Bearing Insect (Amendment) Act 2000 comes into operation effective 1 January 2001. Section 18(d) of the Prevention and Control of Infectious Disease Act 1988 which has provision for the closure of premises found harbouring disease-bearing insects, is used to supplement DDBIA.

7 DISCUSSION

Our review found several studies evaluating varying interventions on dengue incidence. Larviciding and community based strategy; combined community based environmental control and water container cover as well as house screening reduced the rate of dengue incidence (RR=0.19, OR=0.22, OR=0.22) respectively. Significant negative association found between the use of mosquito coils and knock-down spraying (insecticide aerosol). Higher odds of dengue incidence could possibly be in households in which the tools may have been purchased in response to actual increase in mosquito numbers or a dengue case in the neighbourhood during dengue transmission period. Alternately, the householders may have relied solely on these devices, without adopting other preventive and control measures.[39]

We also found three entomological indices widely employed as outcome measures; the BI, CI and HI. With regard to BI, the pooled RE ranged from 0.24 (chemical control, outdoor adulticide) to 0.71(environmental management consisted of environmental modification, environmental manipulation, modification of human habitat or behaviour to reduce human-vector contact). Pooled relative effectiveness for CI ranged from 0.17 (IVM; combination of EM and chemical control) to 0.43 (EM). Meanwhile, pooled RE for HI ranged from 0.12 (IVM; EM and chemical control) to 0.49 (EM). Pooled RD of -0.13, -0.03 was demonstrated effective in reducing BI and CI following community participation. Ecohealth approach, integrated community based (eco-bio-social strategies) reduced BI in Brazil, Equador and Thailand (reduction of CI as well).

Our results highlighted wide variation in the intervention and components being addressed in the included studies. In the review, the RE using integrated approach to reduce the entomological indices was significantly better than the use of single strategy, suggesting combining interventions produce higher overall effect. Moreover, integrated approach covered larger area and population, and hence the observed effect might be higher.[20] Integrated approach is likely to be more sustainable as interventions are community based aiming to change behaviour and induce social mobilisation.[68]

Nevertheless, according to Focks DA et al. (2000), RE, defined as proportion of vector population reduction in relation to pre-intervention level or control area without intervention, do not necessarily equate to effective reduction in pathogen transmission. It is when vector densities fall below critical threshold that transmission rates begin to decrease in response to further decrease in vector density. Dengue transmission threshold is a function of many factors, but key determinants include measures of vector density such as number of pupae per person, and non-vector related factors such as number and size of viral introductions during the year, seroprevalence of dengue antibody and temperature.[37]

In Malaysia, IVM for Dengue prevention and control has been implemented with these strategies, reprioritising *Aedes* surveillance areas; strengthening information system for effective disease surveillance and response, the Communicable

Disease Control Information System; legislative changes; community participation and intersectoral collaboration - national cleanliness and antimosquito campaigns as well as change of insecticide fogging formulation from malathion to water-based pyrethroid (resigen and aqua resigen) and mass abating using Abate. Hence, these components suit the key elements for successful implementation of IVM suggested by the Global Strategic Framework for IVM namely integrated approach, evidence-based decision making, advocacy, mobilisation and legislation as well as collaboration.[69]

Most of the included studies measure impact of intervention on vector indices alone, rather than dengue incidence. However, the classical entomological indices, the CI, BI and HI are imprecise proxy measures for dengue transmission potential.[20] These larval indices have poor correlation with dengue transmission.[39]

There was scarce evidence on impact of IVM strategies on dengue transmission. It remains to be determined how best practices would be defined in any setting to have impact on dengue virus transmission, and not only focusing on entomological indices. There was also inadequacy on appropriately designed trials to evaluate insecticide fogging for the prevention of dengue transmission and dengue incidence. Hence, it is difficult to ascertain effectiveness of space spraying programme in terms of treatment frequency and geographic area requiring treatment. Demonstration on impact of varying interventions on vector population has been reported, but there is no guarantee this will translate into reduction in dengue transmission.[4]This is particularly true for dengue where the complex relationship between vector abundance, virus transmission and human infection rates are unclear.[69]

The WHO Global Strategic Framework for IVM highlighted the importance of IVM in strengthening vector control that is compatible with many health systems.[69] The Strategic Framework for IVM (published in 2004) entails the use of a range of vector control intervention of proven efficacies through collaboration.Such intersectoral and interprogrammatic approaches improve the efficacy, cost-effectiveness, ecological soundness and sustainability of disease-vector control. The application of one evidence-based or selective intervention in integrated manner, competent public health legislation, sound pesticide management policy are integral to IVM. Through evidence-based decision making, IVM rationalises the use of human, financial resources and organizational structures for the vector control and emphasize engagement of communities to ensure sustainability. The IVM implementation should begin with situational analysis (epidemiological, entomological, insecticide resistance status, policy frameworks) and vector control needs assessment (technical, financial, operational needs). Next steps are setting goals, selecting priority diseases, choosing appropriate interventions and stratification of targeted area. Further steps include advocacy and intersectoral collaboration, communication and social mobilization, bulding institutional capacity and facilitating capacity building of other sectors. Monitoring and evaluation are essential components of IVM. Monitoring measures the implementation of its range of activities (the process), while evaluation measures the extent to which direct outcome have been achieved. The input and process required to deliver each intervention must be assessed for effectiveness, cost-effectiveness and sustainability in a given situation.[71] Though the WHO has been actively involved in developing strategies for prevention and control of dengue since 1970s, up to now it is still being reemphasised among the WHO priorities. Vector control has mainly relied on the use of chemical insecticides, which influenced by human, technical, operational, ecological and economic factors. Environmental concern, cost and issues on insecticide resistance has put emphasis on the need for additional vector control involving environmental management, biological control, and community participation.[70] IVM has been documented in several published guidelines for the diagnosis, treatment, prevention and control of dengue.[9,35,71,72]

Similarly, the US CDC highlighted that vector surveillance is a key component of any local IVM programme. The goal of vector surveillance is to quantify human risk by determining local vector presence and abundance. Its principle function are to determine the vector presence in a geographical area, identify type of containers producing the most mosquitoes, collect vector population data, monitor effectiveness of control effort and collect data on infection rates during outbreak. [30]

Likewise, the Vector Borne Disease Control Programme, Ministry of Health and Family Welfare India in the guideline on IVM for the control of DF/DHF addressed the vector control was be made up of environmental management (EM), personal protection, chemical control, biological control, legislative measures and health education for community mobilization and inter-sectoral convergence. Major EM method used for control of immature stage of the vector includes environmental modification (long lasting physical transformation of vector habitats like improved water supply, mosquito proofing of overhead tanks, cisterns); environmental manipulation (temporary changes to vector habitats that involve the management of essential and non-essential containers and management of or removal of natural breeding sites) and changes in human habitations (efforts are made to reduce man-virus contact by mosquito proofing of houses with screens on doors/windows). (India) In 1980, the WHO Expert Committee on Vector Biology and Control defined these three types of environmental management.[73]

The Centre of Health Protection, Department of Health, Hong Kong also highlighted integrated mosquito management approach should be adopted for getting an effective and efficient control on mosquito with minimal impact on the ecological system. One or more measures could be selected from the biological, environmental and chemical categories for controlling the target species.[74]

The limited success in controlling vector-borne disease, mainly due to not being able to reduce the mosquito population below the transmission threshold, calls for development of new and effective control tools. Lee HL et al. (2015) highlighted new tools aiming at reducing the vector population below the low dengue transmission threshold; namely insecticide-based (i) Outdoor residual spraying ii) Autodissemination trap iii) Insecticide with both adulticiding and larviciding property iv) Insecticidal emulsion paint; biological based i) Wolbachia ii) *Bacillus thuringiensis H-14*; gene based i) genetically modified *Aedes Aegypti* ii) Sterile Insect Technique; mechanical based i) Autocidal trap and environmental based i) Dengue outbreak prediction model (mathematical model validated with epidemiological, ecological and entomological data).[75]

Dengue control is a challenging endeavour especially because *Aedes aegypti* evolves in response to control intervention (development of insecticide resistance), because herd immunity is affected by reduced transmission associated with control, and because viral reintroduction can occur from other locations, making dengue elimination unlikely. Hence, the consideration of disease transmission dynamic and insecticide resistance is important in implementing insecticide-based dengue vector control programme in a specific setting. More studies of insecticide delivery, efficacy and effect are needed as they would be important for the guidance of future economic analysis of vector control. [56]

7.1 LIMITATION

The systematic review of literature has several limitations. There were limited studies on IVM for disease incidence. Combination of strategies applied in the IVM approach varies widely in the studies included. Generalisability of the retrieved evidence could be restricted. The term IVM refers to strategy or framework rather than a particular intervention hence limit inclusion of studies in this review. New tools or methods for Aedes control would not be able to be addressed in this review if it was conducted alone without other IVM strategies. Newer intervention to control *Aedes*, namely vaccine was excluded from the scope of this review. Although there was no restriction in language during the search but only English full text articles were included. There was considerable overlap in the studies included in the SR in this review. We did not conduct a rigorous assessment of the concordance of the data reported in the SR with those stated in the primary studies. In the economic studies, direct comparison between studies was fairly difficult as the assumptions and model parameters varied.

8 CONCLUSION

Effectiveness

There was fair level of retrievable evidence on effectiveness of IVM for Aedes control.

Combination of larviciding and community based strategy; combined community based environmental control and water container cover; as well as house screening reduced the rate of dengue incidence (RR=0.19, OR=0.22,OR=0.22) respectively.

Three entomological indices were widely used as outcome measures; the BI, CI and HI. With regard to BI, the pooled RE ranged from 0.24 (chemical control, outdoor adulticide) to 0.71(environmental management consisted of environmental modification, environmental manipulation, modification of human habitat or behaviour to reduce human-vector contact). Pooled RE for CI ranged from 0.17 (IVM; combination of EM and chemical control) to 0.43 (EM). Meanwhile, pooled RE for HI ranged from 0.12 (IVM; EM and chemical control) to 0.49 (EM). IVM (combination of EM and chemical control) was the most effective method to reduce the CI,HI, BI with the above results. Community participation was effective in reducing BI and CI, with pooled RD of -0.13, -0.03. Integrated Vector Management

(EM and chemical control) had the largest number of population covered (median population size of 12,450; ranged from 210 to 9,600,000).

Eco-bio-social (integrated community based) intervention was effective in significantly reducing overall PPI values in intervention cluster (-85.1%) compared to control cluster (-47.2%, p<0.001).

Performance analysis of different control strategies showed all category of interventions (biological, chemical, integrated) contributed significantly to the control of *A aegypti* (p<0.0001), with integrated intervention demonstrated as the most effective method.

For sustainability of programme, the community-based strategy adopted in the studied community was rated as well-sustained, sustainability scores ranged from 4.20 to 4.42.

Safety
There was no retrievable evidence on the safety of IVM for *Aedes* control.

Cost-effectiveness
There was limited retrievable evidence on economic evaluation of IVM for *Aedes* control.

Evidence demonstrated there was variation in the ICER for different strategy; following community participation was $3952.84 per DALY avoided, using two applications of high-efficacy adult control was $615 per DALY saved; whereas ICER for the use of six applications of high-efficacy adult control was $1267 per DALY saved. The strategy using two applications of high-efficacy adult control per year was the most cost-effective (cost minimisation strategy), and using six applications of high-efficacy adult control per year was the most cost-effective (benefits maximisation strategy) . The community-based approach was more cost-effective compared to vertical programme from health system perspective (US$964 versus US$ 1406 per focus) as well as from society perspective (US$1508 versus US$1767 per focus).

The total economic cost per inhabitant per months increased from USD2.76 in months without transmission to USD6.05 during an outbreak for dengue control and management, equivalent to an increase in the average monthly cost from USD 673,959 (in month without transmission) to USD 1,477,617 (during an outbreak), amounted to 0.7% of the country's monthly GDP in period without transmission to 1.5% in the period with transmission.

Malaysia spent an estimated US$73.5 million (95%CI US$million 62.0, 86.3) for the national dengue vector control, constituting 0.03% of the country's GDP in 2010 (US$247.5billion), 92.2% of these costs were incurred at District Health Department level, human resources costs made up 64.8% of total national vector control costs while pesticide, fogging equipment, PPE, and outsourced fogging activity made up 19.4% of the total national vector control cost.

Financial implication
In Malaysia, over three years (2016 to 2018), the proportion of total cost saving from reduction of dengue cases (MYR 101million) relative to total cost of integrated dengue vector control (MYR 772 million) was approximately 13.08%.

There was also minimal reduction (15.07%) in cost-related to dengue illness (MYR 101 million) relative to the estimated annual economic burden of dengue illness demonstrated over three years (MYR 670 million).

As of 8th May 2019, the total dengue cases reported was 45,660. Therefore, estimated total cost of dengue illness is MYR 116 million (May 2019), and MYR 348 million (December 2019), with the cost of vector control in 2019 estimated to remain as in 2018 (MYR 260 million).

Social
There was fair level of retrievable evidence on social implications of IVM for Aedes control.

Following integrated eco-bio-social intervention, higher percentage of people in the treatment clusters agreed that applying *copepods* and *Bti* to water-holding containers was not complicated, compared to the control clusters (67.1% vs. 52.1%, p=0.006). The percentage of people in the treatment clusters who agreed that it was only health volunteers who were responsible for dengue prevention in the community was significantly lower than in the control clusters (12.9% vs. 26.1%, p=0.013).

The community centred ecosystem management resulted in better community knowledge, attitude and practices in dengue prevention, increased household and community participation, improved partnership including a variety of stakeholders with prospects for sustainability, vector control efforts refocused on environmental and health issues and increased community ownership on dengue vector management.

Organizational
Capacity building, in particular human resource development is a major prerequisite, because the IVM strategy requires skilled staff and adequate infrastructure at central and local levels. Core functions and essential competency required for IVM at central and local levels required are outlined in the core structure for training curricula on integrated vector management.

The IVM must be actively advocated and communicated to ensure continued support. The general public must be made aware of the strategy and participate in its implementation. Communications for reaching them should lead to behavioural change and empowerment.

The IVM requires collaboration of various agencies and community participation in assuring sustainability. To foster sustainability, interventions must focus on capacity building in the recipient community. Institutionalization is a key process on the path toward sustainability.Though it is challenging to involve the population in the control efforts, any measure adopted should be based more on community involvement than on vertical approaches.

Health services personnel should be able to interact effectively with residents, and have role as health promoters and evaluators, while undertaking entomological surveillance and vector control. Emphasizing communication and interpersonal communication may transmit more appropriate messages for behaviour modification.

Ethical

The approach to genetically modified (GM) vectors for disease control raises few intrinsic ethical issues. Important environmental and human health concerns need to be assessed before release of any GM vectors, as there are concerns over unknown long term effect in human and the ecosystem.

Legal

Within the European Union, legislation of mosquito control agent is implemented through the Biocidal Product Directive (BPD)(98/8/EG) and the Biocidal Product Regulation (EU) No.528/2012. In Malaysia, established legislations to cover the prevention and control of vector-borne diseases are; i) Destruction of Disease-Bearing Insect Act (DDBIA) 1975 (Act 154), ii) Prevention and Control of Infectious Disease Act 1988 (Act 342), and iii) Local Government Act 1976 (Act 171).

9 RECOMMENDATION

Based on the above review on IVM for *Aedes* control, strategies using combination of environmental management, chemical control and community based activities reduced entomological parameter and rate of dengue incidence. Community based activity has good social acceptance and contribute towards sustainability of IVM. Chemical control using six applications of high-efficacy adult control per year was the most cost-effective method (benefit maximisation strategy). Hence, the current IVM strategy for *Aedes* control may need to be further strengthened in its implementation.

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Appendix 1

HIERARCHY OF EVIDENCE FOR EFFECTIVENESS STUDIES

DESIGNATION OF LEVELS OF EVIDENCE

I Evidence obtained from at least one properly designed randomized controlled trial.

II-I Evidence obtained from well-designed controlled trials without randomization.

II-2 Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one centre or research group.

II-3 Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.

III Opinions or respected authorities, based on clinical experience; descriptive studies and case reports; or reports of expert committees.

SOURCE: US/CANADIAN PREVENTIVE SERVICES TASK FORCE (Harris 2001

Appendix 2

PTK – FM – 02

HEALTH TECHNOLOGY ASSESSMENT (HTA) PROTOCOL
INTEGRATED VECTOR MANAGEMENT FOR *AEDES* CONTROL

1. BACKGROUND INFORMATION

Aedes aegypti, a cosmotropical mosquito that thrives in urban environment, is a vector of international concern as it transmits to humans important arboviral diseases; dengue, yellow fever, zika and chikungunya.[1-4] It is highly anthropophilic and can also breed in small amount of clear water. The success of Aedes aegypti is linked to its opportunistic and high adaptability to the peridomestic environment exploiting any stagnant water as its breeding habitat.[5] Aedes albopictus, was originally confined to Asia, but now has expanded its global range and contributed to the spread of chikungunya and dengue virus.[6] Four main infections spread by Aedes aegypti and Aedes albopictus; dengue, yellow fever, chikungunya and zika cause considerable morbidity, mortality and healthcare expenditure in low and middle-income countries.[7]

The main one of these is still dengue, with incidence grown dramatically around the world in recent decades.[8] Dengue is the most important arboviral disease globally and the fastest emerging arboviral infection.[9] Today, the disease is endemic in more than 100 countries in five WHO regions; with the Americas, South-East Asia and Western Pacific regions are the most seriously affected. The number of cases from these three regions reported an increase from 2.2 million (2010) to 3.2 million (2015).[8] Among an estimated 2.5 billion people at risk globally, about 1.8 billion (more than 70%) reside in Asia Pacific.[9] Its epidemiology is rapidly evolving with more than 50% of the world's population lives in regions at risk of the disease, and evidence points towards further geographical and numerical expansion.[10] The global increase of dengue incidence is also experienced by Malaysia with reported incidence of 30.2 cases per 100,000 population (2000) to 261.6 cases per 100,000 population (2017).[11] Dengue has high social and economic impact, affecting not just the patient, but also families and the community. In the Americas, an estimated economic cost of the disease supersedes US$2.1billion per year.12 In Malaysia, an estimated US$73.5million in public funds or 0.03% of the country's GDP was spent on its National Dengue Vector Control Programme, which represented US$1,591 per reported dengue case (2010).[13]

Various strategies for vector control exists and have been used for decades, using chemical, physical, biological, or an integrated approach.[14] Dichlorodiphenyltrichloroethane (DDT) was one of the first chemical measures used to target adult dengue vectors. Subsequent DDT resistance led to dengue re-emergence followed by introduction of second and third generation insecticides (e.g. malathion and pyrethroids).[15] The use of DDT is banned since 1998 in Malaysia.[16] Chemical control nevertheless has shortcomings, including environmental contamination, bioaccumulation of toxins, concerns on human toxicity and emergence of resistance to insecticides in target species.[17,18] Alternative methods consist of biological control (e.g. the introduction of larvivorous organisms such as fish, copepods and insect larvae into water containers), release of transgenic vectors (aimed at reducing or even replacing the wild-type vector population with one that has a reduced capacity to transmit and reproduce) and environmental management (e.g. source reduction, provision of safe water, covering and screening of water containers, and reduction of human-vector contact by screening doors and windows and using insecticide-treated nets) were introduced.[19] Factors influencing the transmission of dengue such as the virus, the human as the host, the vectors, unsatisfactory environmental condition and climate change, with rapid urbanisation, population growth and international travel, creates challenge in the efficient control of the disease. Integrated Management Strategy for the Prevention and Control of Dengue (IMS-Dengue) as highlighted by World Health Organisation (WHO) consisted of strengthening epidemiological surveillance, laboratory networks, integrated vector management (IVM), clinical management of patients, environmental management and social communications.[20] World Health Organisation promotes the strategic approach known as IVM to control mosquito vectors. Integrated vector management (IVM) is defined as a rational decision-making process for the optimal use of resources for vector control, aiming to improve efficacy, cost-effectiveness, ecological soundness and sustainability of disease-vector control with ultimate goal to prevent vector-borne diseases transmission including dengue. The Global Strategic Framework for IVM identifies five key elements for its successful implementation:-[21]

- Integration of non-chemical and chemical vector control methods, and integration with other disease control measures
- Evidence-based decision making guided by operational research and entomological and epidemiological surveillance and evaluation
- Advocacy, social mobilisation, regulatory control for public health and empowerment of communities
- Collaboration within the health sector and with other sectors through the optimal use of resources, planning, monitoring and decision-making
- Development of adequate human resources, training and career structures at national and local level to promote capacity building and manage IVM programmes

Integrated vector management comprises two or more strategies employed simultaneously.[4] Some forms of IVM, including chemical control, community involvement, and co-operation between services have been said as among the effective approach to reduce Aedes aegypti infestation or control dengue outbreaks.[19]

In Malaysia, IVM for Dengue prevention and control has been implemented with these strategies:- [22]

- Reprioritising Aedes surveillance areas

Prior to 1998, Aedes larval surveys were concentrated in residential areas though Aedes breeding was demonstrated to be low, at around or below 1% of houses inspected. In contrast, surveillance at construction sites indicated Aedes index to be very high. Thus, in 1998, the approach was changed where dengue teams carried out regular inspections at construction sites, factories, abandoned housing projects, garbage dump sites, schools, government facilities and others, besides inspections at any site during case/outbreak investigations. Targets were set in terms of proportions of different premises and areas to be inspected, based on three classifications of priority areas.

- Strengthening information system for effective disease surveillance and response Communicable Disease Control Information System (CDCIS)

Comprehensive national computerised CDCIS provides platform for systematic reporting of disease notification, disease registration, case investigations, case follow-up, and early warning system.

- Legislative changes

The main legislative control, Destruction of Disease-Bearing Insects Act, 1975, was amended and new provisions for heavier penalties became enforceable from January 2001. This amendment aimed at big offenders such as housing developers and factory owners where the earlier penalty was not deterrent enough.

- Community participation and intersectoral collaboration - national cleanliness and antimosquito campaigns

In 1999, the Government reaffirmed its commitment towards the control of mosquito-borne diseases such as dengue by the launching of a multi-ministerial National Cleanliness and Anti-Mosquito Campaign.

- Changing insecticide fogging formulation and mass Abating

Traditionally, malathion was the chemical of choice for dengue control in Malaysia. However, the acceptance of fogging inside houses was low as malathion has unpleasant smell and diesel-solvent left oily residues on the floors and walls of the houses. The use of malathion was stopped in 1996 and replaced with water-based pyrethroid fogging formulations such as Resigen and Aqua-resigen. In 1998, use of Abate larvicide on a large scale in high-risk areas was initiated to reduce Aedes larval density.

Despite decades of control programme, mosquito population is still abundant and dengue incidence persists with outbreaks occuring in affected communities worldwide.[23] Besides, it was said that there was no evidence that vector-control efforts such as massive use of insecticides have significant effect on dengue transmission.[24]The recognition of the link between zika virus and microcephaly recently led to renewed global interest in Aedes control.[23] Thus, the need for evidence-based selection of the most appropriate, cost-effective and environmentally save interventions for Aedes control has never been greater. Therefore, the purpose of this Health Technology Assessment (HTA) is to evaluate the evidence of effectiveness, safety and cost-effectiveness, organisational, social and ethical implications of IVM for Aedes control in Malaysia. This assessment was requested by the Head of Vector Borne Disease Sector, Disease Control Division, Ministry of Health.

2.0 POLICY QUESTION:

Which IVM strategies will be the most effective, safe and cost-effective approach for Aedes control in Malaysia?

3.0 OBJECTIVES:

3.1 The following are the objectives of this review:

i. To determine the effectiveness of IVM for Aedes control compared with no comparator or other control measures
ii. To determine the safety of IVM for Aedes control compared with no comparator or other control measures
iii. To determine the economic, social, organisational, ethical and legal implications of IVM for Aedes control

3.2 The following are the research questions of this review:

i. What is the effectiveness of IVM for Aedes control compared with no comparator or other control measures?
ii. How safe is IVM for Aedes control compared with no comparator or other control measures?
iii. What are the economic, organisational, social, ethical and legal implications of IVM for Aedes control?

4. METHODS

Systematic reviews following the principles used by Cochrane Collaboration will be conducted to achieve the objectives of this review

4.1. Search Strategy

i. Electronic database will be searched for published literatures pertaining to breast cancer risk assessment/prediction models among women, its performance, accuracy, benefits, strengths and weaknesses, implications
ii. The following databases will be used to carry out the search of evidence:- MEDLINE, EBM Reviews-Cochrane Database of Systematic Review, EBM-Reviews-Cochrane Central Register of Controlled Trials, EBM Reviews-Health Technology Assessment, EBM Reviews-Cochrane Methodology Register, EBM Reviews-NHS Economic Evaluation Database, Database of Abstracts of Reviews of Effects (DARE), PubMed, Horizon Scanning, INAHTA Database, HTA database and FDA database.
iii. Additional literatures will be identified from the references of the relevant articles.
iv. Expert in this area will be contacted when necessary to get further information.
v. Handsearching of evidence will be conducted if necessary to find unpublished evidence
vi. General search engine might be used to get additional web-based information if there is no retrievable evidence from the scientific databases.
vii. There will be no limitation applied in the search such as year and language.
viii. The detail of the search strategy will be presented in the appendix.

4.2 Inclusion and exclusion criteria

4.2.1 Inclusion criteria

Population Problems	*Aedes aegypti, Aedes albopictus, Aedes sp*., mosquito, vector
Intervention	• Integrated vector management, combined vector control/strategies (two or more out of five IVM elements) • Existing control (IVM) and additional control method
Comparators	• No comparator • Chemical control (indoor and outdoor spraying/fogging, residual spray with insecticides, container treatment with larvicides and lethal ovitraps/autodissemination trap; chemical insecticides belongs to pyrethroids, organophospates, organochlorine, carbamates,insect growth regulators) • Biological control [(larvivorous fish, insect predators, crustaceans (copepods), bacteria based *Bacillus thuringiensisvar israelensis, Bti*], • Physical/mechanical control (regular cleaning of containers, container covers and ovitraps) • Environmental management • Community mobilisation • Health education • Punitive methods via the legal systems • Mosquito population control methods [(use of *Wolbachia spp*., genetic manipulation of mosquito (e.g.introduction of sterile males)] • Adult trapping (BG trap, sticky trap, light trap, CO_2 trap) • Collaboration • Existing control (IVM)

Outcomes	i. Effectiveness of IVM for *Aedes* control
	• Entomological infestation indices/parameters:
	  o Breteau Index (BI): Number of positive containers with *Aedes sp* larvae per 100 houses
	  o Household Index (HI)/Aedes Index (AI): Percentage of houses positive with immature (larvae/pupae or both)
	  o Container Index (CI): percentage of containers specifically designed for water storage positive for immature (larvae/pupae)
	  o Mosquito density (number of adult mosquitoes per number of houses surveyed)
	  o Ovitrap positivity rate (number of mosquito traps with eggs, divided by total number of traps multiplied by 100)
	  o Pupae index (number of pupae per 100 houses inspected)
	• Incidence/cases of Dengue/vector-borne disease caused by *Aedes sp*
	• Mortality from Dengue/vector-borne disease caused by *Aedes sp*
	• Larva density (mean number of larva per container)
	• Mosquito mortality rate
	• Pupae per person index (number of pupae collected per human population in a sector)
	
	ii.Safety of using IVM for *Aedes* control
	• Any reported adverse outcome or unintended consequences on people or the environment

	iii. Cost analysis, cost-effectiveness, cost-utility of IVM for *Aedes* control iv. Organisational, social, ethical and legal implications of IVM for *Aedes* control
Study designs	HTA reports, systematic review with meta-analysis, systematic review, randomised controlled trial (RCT), non-randomised trial, cohort, case-control, cross-sectional and economic evaluation studies
English full text articles	

4.2.2 Exclusion criteria

- Studies with these design will be excluded:
  - i. Animal study
  - ii. Narrative review
  - iii. Laboratory study
- Non English full text article.

4.3 Data extraction strategy

The following data will be extracted:

i. Details of methods and study population characteristics.
ii. Details of interventions and comparators.
iii. Details of individual outcomes for effectiveness, safety and cost associated with LDCT for lung cancer screening.

Data will be extracted from selected studies by a reviewer using a pre-designed data extraction form and checked by another reviewer. Disagreements will be resolved by discussion

4.4 Quality assessment strategy/Assesment of risk of bias

The validity of the eligible studies will be assessed by two reviewers independently using Critical Appraisal Skill Programmes checklists criteria according to the study designs.
The quality of the evidence will be graded according to US/Canadian Preventive Services Task Force Grading System.

4.5 Methods of analysis/synthesis

Data on the effectiveness, safety and cost-effectiveness of LDCT for lung cancer screening will be presented in tabulated format with narrative summaries. No meta-analysis will be conducted for this Health Technology Assessment.

5 REPORT WRITING

Appendix 3

Search strategy

MEDLINE ® Epub Ahead of Print **In progress and other Non-Indexed Citations and Ovid Medline® 1946 to present.**

1 AEDES/ (13366)
2 aede*.tw. (14366)
3 mosquito*.tw. (37394)
4 insect vector*.tw. (1873)
5 larva*.tw. (90355)
6 Dengue.tw. (18176)
7 Chikugunya.tw. (10)
8 Zika.tw. (4531)
9 Yellow fever.tw. (5135)
10 MOSQUITO CONTROL/ (8205)
11 mosquito control.tw. (1669)
12 PEST CONTROL, BIOLOGICAL/ (9496)
13 biologic* pest control*.tw. (119)
14 (biologic* adj pest control*).tw. (119)
15 Insecticide*.tw. (27793)
16 (integrated adj delivery system*).tw. (745)
17 (integrated adj health care system*).tw. (528)
18 integrated vector management.tw. (204)
19 (integrated adj vector management).tw. (204)
20 1 or 2 or 3 or 4 or 5 (126992)
21 6 or 7 or 8 or 9 (25257)
22 20 and 21 (7814)
23 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (43766)
24 22 and 23 (1655)
25 limit 24 to (english language and humans) (702)

EMBASE

1 AEDES/ (5216)
2 aede*.tw. (11641)
3 mosquito*.tw. (32975)
4 insect vector*.tw. (1591)
5 larva*.tw. (68742)
6 Dengue.tw. (20312)
7 Chikugunya.tw. (13)
8 Zika.tw. (4847)
9 Yellow fever.tw. (3859)
10 MOSQUITO CONTROL/ (594)
11 mosquito control.tw. (1876)
12 PEST CONTROL, BIOLOGICAL/ (7611)
13 biologic* pest control*.tw. (111)
14 (biologic* adj pest control*).tw. (111)
15 Insecticide*.tw. (23541)
16 (integrated adj delivery system*).tw. (715)
17 (integrated adj health care system*).tw. (694)
18 integrated vector management.tw. (236)
19 (integrated adj vector management).tw. (236)
20 1 or 2 or 3 or 4 or 5 (99285)
21 6 or 7 or 8 or 9 (26284)
22 20 and 21 (8249)
23 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (33599)
24 22 and 23 (1167)
25 limit 24 to (english language and humans) (435)

EBM Reviews - Cochrane Database of Systematic Reviews

1. [AEDES/] (0)
2 aede*.tw. (6)
3 mosquito*.tw. (64)
4 insect vector*.tw. (4)
5 larva*.tw. (44)
6 Dengue.tw. (25)
7 Chikugunya.tw. (0)
8 Zika.tw. (2)
9 Yellow fever.tw. (13)
10 [MOSQUITO CONTROL/] (0)
11 mosquito control.tw. (13)
12 [PEST CONTROL, BIOLOGICAL/] (0)
13 biologic* pest control*.tw. (0)
14 (biologic* adj pest control*).tw. (0)
15 Insecticide*.tw. (48)
16 (integrated adj delivery system*).tw. (0)
17 (integrated adj health care system*).tw. (7)
18 integrated vector management.tw. (4)
19 (integrated adj vector management).tw. (4)
20 1 or 2 or 3 or 4 or 5 (96)
21 6 or 7 or 8 or 9 (34)
22 20 and 21 (10)
23 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 (56)
24 22 and 23 (3)
25 22 and 23 (3)

Appendix 4

CRITICAL APPRAISAL SKILLED PROGRAMME CHECKLIST

SYSTEMATIC REVIEW

CRITERIA ASSESSED			
Authors look for the right type of papers?	Yes ☐	No ☐	Can't tell ☐
Selection of studies (All relevant studies included?)	Yes ☐	No ☐	Can't tell ☐
Assessment of quality of included studies?	Yes ☐	No ☐	Can't tell ☐
If the results of the review have been combined, is it reasonable to do so? (heterogeneity)	Yes ☐	No ☐	Can't tell ☐

RCT

CRITERIA ASSESSED			
Assignment of patients randomised?	Yes ☐	No ☐	Can't tell ☐
Allocation concealment?	Yes ☐	No ☐	Can't tell ☐
Patients, health workers, study personnel blind to treatment?	Yes ☐	No ☐	Can't tell ☐
Were groups similar at the start of the trial?	Yes ☐	No ☐	Can't tell ☐
Were the groups treated equally?	Yes ☐	No ☐	Can't tell ☐
Were all of the patients who entered the trial accounted for at its conclusion? - Intention to treat analysis - Explanation of loss to follow-up	Yes ☐	No ☐	Can't tell ☐

COHORT

CRITERIA ASSESSED			
Selection (cohort recruited in an acceptable way?)	Yes ☐	No ☐	Can't tell ☐
Exposure accurately measured?	Yes ☐	No ☐	Can't tell ☐
Outcome accurately measured to minimise bias?	Yes ☐	No ☐	Can't tell ☐
Confounding factors identified and taken account?	Yes ☐	No ☐	Can't tell ☐
Follow-up of subjects complete and long enough?	Yes ☐	No ☐	Can't tell ☐

PRE-POST INTERVENTION STUDIES

CRITERIA ASSESSED			
Question or objective clearly stated?	Yes ☐	No ☐	Other CD,NA,NR ☐
Eligibility/selection criteria for study population clearly described?	Yes ☐	No ☐	Other CD,NA,NR ☐
Were participants representative for those who would be eligible for the test/service/ intervention in the population of interest ?	Yes ☐	No ☐	Other CD,NA,NR ☐
Were all eligible participants that met the prespecified entry criteria enrolled?	Yes ☐	No ☐	Other CD,NA,NR ☐
Sample size sufficiently large to provide confidence in findings?	Yes ☐	No ☐	Other CD,NA,NR ☐
Test/service/intervention clearly described and delivered consistently?	Yes ☐	No ☐	Other CD,NA,NR ☐
Outcome measures prespecified, valid, reliable, and assessed consistently?	Yes ☐	No ☐	Other CD,NA,NR ☐

People assessing the outcome measures blinded to participants exposure/interventions?	Yes ☐	No ☐	Other CD,NA,NR ☐
Loss to follow-up after baseline 20% or less? Loss to follow-up accounted for in the analysis?	Yes ☐	No ☐	Other CD,NA,NR ☐
Statistical methods examine changes in outcome measures from before to after intervention? P value?	Yes ☐	No ☐	Other CD,NA,NR ☐
Outcome measures taken multiple times before and after intervention? Use interrupted time-series design?	Yes ☐	No ☐	Other CD,NA,NR ☐
If intervention conducted at group level, did statistical analysis take into account of individual level data to determine effects at group level?	Yes ☐	No ☐	Other CD,NA,NR ☐

ECONOMIC EVALUATION

CRITERIA ASSESSED			
A well-define question posed?	Yes ☐	No ☐	Can't tell ☐
Comprehensive description of competing alternative given?	Yes ☐	No ☐	Can't tell ☐
Effectiveness established?	Yes ☐	No ☐	Can't tell ☐
Effects of intervention identified, measured and valued appropriately?	Yes ☐	No ☐	Can't tell ☐
All important and relevant resources required and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?	Yes ☐	No ☐	Can't tell ☐
Costs and consequences adjusted for different times at which they occurred (discounting)?	Yes ☐	No ☐	Can't tell ☐
Results of the evaluation?	Yes ☐	No ☐	Can't tell ☐
Incremental analysis of the consequences and costs of alternatives performed?	Yes ☐	No ☐	Can't tell ☐
Sensitivity analysis performed?	Yes ☐	No ☐	Can't tell ☐

Appendix 5

Evidence Table : Effectiveness
Question : Is IVM effective for *Aedes* control?

<table>
<tr><th>Bibliographic citation</th><th>Study Type / Methods</th><th>LE</th><th>Number of patients and patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow up (if applicable)</th><th>Outcome measures/ Effect size</th><th>General comments</th></tr>
<tr>
<td>1. Bowman LR, Donegan S, McCall PJ. Is Dengue vector control deficient in effectiveness or evidence? Systematic review and meta analysis. PLoS Negl Trp Dis 2016;10(3):e0004551.doi:10.1371/journal.pntd.0004551

Liverpool School of Tropical Medicine, Liverpool, UK</td>
<td>Systematic review and meta analysis

Objective
To review randomised and non-randomised studies to evaluate effectiveness of vector control intervention in reducing Aedes sp indices and human DENV infection/disease.

Method
Studies of any design published since 1980 were included if they evaluated control methods (singly or combined) targeting Ae aegypti or Ae albopictus for at least 3 months (minimum period required to demonstrate a sustained impact on vector population/dengue transmission).
Outcome: dengue incidence and/or entomological indices (Breteau Index(BI), House Index (HI), Container Index (CI), tank positivity, number of mosquito adults, pupae per person index (PPI), presence of Aedes immature and ovitrap</td>
<td>I</td>
<td>Included studies, n=41
• RCT (9; 2 RCT,7 cluster randomised trial),
• non randomised studies (32; 8 controlled trial, 7 longitudinal studies, 4 interrupted time series, 5 before and after studies, 6 observational studies, 2 models).

South east Asia (11), South Asia (8), Australasia (4), South America (5), Central America (10), North America (3)</td>
<td>Combined intervention or single intervention for Aedes aegypti /albopictus control used for >3months

Frequently evaluated intervention were clean up programme, outdoor fogging, education, larviciding, water jar covers</td>
<td>-</td>
<td>Ranged from 5 months to 10 years</td>
<td>• Dengue incidence
Combined community based environmental management together with use of water container covers reduced odds of dengue incidence 0.22 (95%CI 0.15,0.32), house screening reduced the odds of dengue incidence with pool OR 0.22 (95%CI 0.15,0.32) compared to homes without screens

<table>
<tr><th>Intervention</th><th>References</th><th>pool OR (95%CI)</th></tr>
<tr><td>Knockdown spray</td><td>McBride 1998</td><td>2.03 (1.44,2.86)</td></tr>
<tr><td>House screening</td><td>MurraySmith 1996
McBride 1998</td><td>0.22 (0.05,0.93)</td></tr>
<tr><td>Indoor residual spraying</td><td>V Prokopec 2010
Ko 1992</td><td>0.67 (0.22,2.11)</td></tr>
<tr><td>EM & water lids</td><td>Toledo 2011</td><td>0.22 (0.15,0.32)</td></tr>
<tr><td>Insect repellants</td><td>McBride 1998</td><td>1.02 (0.71,1.47)</td></tr>
<tr><td>Bed nets</td><td>McBride 1998
Ko 1992</td><td>0.91 (0.49,1.67)</td></tr>
<tr><td>Mosquito coils</td><td>Ko 1992
McBride 1998</td><td>1.44 (1.09,1.91)</td></tr>
<tr><td>Mosquito traps</td><td>Ko 1992</td><td>1.18 (0.67,2.08)</td></tr>
</table>
(Heterogeneity, I^2=92.1%), EM=environmental management
Non randomised controlled trial subgroup analysis

• Entomological Indices
- BI
<table>
<tr><th>Intervention</th><th>Ref</th><th>Effect measure (rate ratio/mean diff)(95%CI)</th></tr>
<tr><td>Community based environmental modification, larvicide,</td><td>Vanlerberghe 2010</td><td>0.48* (0.26,0.89)</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

<table>
<tr><th>Bibliographic citation</th><th>Study Type / Methods</th><th>LE</th><th>Number of patients and patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow up (if applicable)</th><th>Outcome measures/ Effect size</th><th>General comments</th></tr>
<tr><td></td><td>positivity rates.
Original search was conducted on April 2012, last search was on 10 January 2015. Databases searched: WHOLIS, MEDLINE, EMBASE, LILACS. PRISMA group guideline was followed as standard methodology. Risk of bias assessment;, Cochrane risk of bias tool used for RCT, while for non-RCT, Quality Assessment Tool for quantitative study (Thomas BH et al 2004) was used. Analysis was performed using RevMan version 5.2</td><td></td><td></td><td></td><td></td><td></td><td>
<table>
<tr><td>water cover, social mobilisation</td><td></td><td></td></tr>
<tr><td>Community based clean up, social mobilisation, education, inspection</td><td>Castro 2012</td><td>0.65*
(0.52,0.81)</td></tr>
<tr><td>Community based env management, water covers, social mobilisation, clean up</td><td>Arunachalam 2012</td><td>-4.66#
(-5.89,-3.43)</td></tr>
</table>
Community based combined intervention significantly reduced BI, HI and CI

- HI
<table>
<tr><th>Intervention</th><th>Ref</th><th>Effect measure (95%CI)</th></tr>
<tr><td>Comm based env modification,larvicide, water cover, soc.mobilisation</td><td>Vanlerberghe 2010</td><td>0.49*
(0.27,0.89)</td></tr>
<tr><td>Comm based clean up, soc mobilisation, education, inspection</td><td>Arunachalam 2012</td><td>-17.10 #
(-22.16,-12.04)</td></tr>
</table>
- CI
<table>
<tr><th>Intervention</th><th>Ref</th><th>Effect measure (95%CI)</th></tr>
<tr><td>Comm based clean up, soc mobilization, education, inspection</td><td>Arunachalam 2012</td><td>-12.30#
(-17.36,-7.24)</td></tr>
</table>
* rate ratio # mean difference
(cluster randomized trial)

• Community based environmental management significantly reduced HI (MD=-2.14(95%CI-3.72,-0.56) and combination interventions (clean up campaign, with IRS and larviciding) reduced ovitrap positivity (MD= -10.30(95%CI-12.80,-7.80).
IRS=indoor residual spraying
</td><td>No pooling of data</td></tr>
</table>

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							• Use of fogging, source reduction and larviciding reduced the odds of detecting increased larval densities, BI [OR=0.15(95%CI 0.10, 0.24)], and HI [OR=0.13(95%CI 0.08, 0.22)] when compared to baseline. **Author conclusion** The review demonstrated paucity of reliable evidence for the effectiveness of any dengue vector control method. Standardised study of higher quality to evaluate and compare methods must be prioritised to optimize cost effective dengue prevention.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
2. Erlanger TE, Keiser J & Utzinger J. Effect of dengue vector control interventions on entomological parameters in developing countries: a systematic review and meta analysis. Medical and Veterinary Entomology 2008;22,203-221 Swiss Tropical Institute, Switzerland	Systematic review and meta analysis **Objective** To compare the effects of different dengue control interventions (ie biological control, chemical control, environmental management and integrated vector management) with respect to the following entomological parameters (BI, CI, and HI). **Methods** Systematic search from PubMed, ISI web of Science, Science Direct, Dengue Bulletin of the WHO and reference list of retrieved articles done up to December 2007. Different dengue control interventions (ie. biological control, chemical control, environmental management (EM) and integrated vector management in developing countries were selected. EM comprises of: i) environmental modification ii) environmental manipulation iii) modification or manipulation of human habitation of behavior to	I	Included studies, n=56 from 23 countries RCT, cluster RCT, non randomised controlled trial, interrupted time series, pre-post intervention study, observational study South east Asia (27), south and east Asia (5), Caribbean (10), central America (8), south America (7), Polynesia (4)	Chemical control (19) Biological control (10) Environmental management (14) IVM: EM plus chemical (8) EM plus biological (10)	-	2.5 months to 20.5 months	**Chemical control** - Used chemicals; temephos (Abate)(7), malathion (4), fanitrothion(4), pyrethoids (3). - Function: larviciding, adulticiding (indoor and outdoor), the latter combination - Meta analysis done only for group use outdoor adulticides measuring BI; (5 studies) - Pool relative effectiveness (RE) =0.24(95%CI 0.05,1.19) for outdoor adulticiding against dengue vector measured by Breteau Index **Biological control** - Organisms used: copepods (Mesocyclops spp)(3), fish (4), predatory insect larvae (Toxorhynchites spp)(2),Crocothemis spp (1). - Pool RE =0.18 (95%CI0.07,0.44) for biological control against dengue vector measured by Container Index (9 studies) **Environmental management** - The most used method: removal of unused water vessels and covering of water containers - Pool RE =0.71(95%CI 0.55,0.90) measured by BI (9 studies) - Pool RE =0.43(95%CI 0.31,0.59) measured by CI (10 studies) - Pool RE =0.49(95%CI 0.30,0.79) measured by HI (10 studies) **Integrated vector management** - Environmental management (EM) combined chemical intervention (13), or biological control (5) - **IVM (combination of EM and chemical control)** was the most effective method to reduce the CI,HI, BI with:- • **Pool RE =0.12(95%CI 0.02,0.62)**	No standard methdology e.g. PRISMA followed, nor risk of bias assessment

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	reduce human-vector contact. Inclusion: studies from less & medium developed countries (Human Development Index ≤0.8, UNDP 2008), with 4 exceptions: Cuba, Mexico, Trinidad & Tobago. Study from longitudinal or cross sectional surveys included. Studies under laboratory or semi field condition were excluded. Only studies with data could be transformed into BI, CI, HI or dengue incidence included. **Relative Effectiveness (RE) is defined as proportion of vector population reduction in relation to pre-intervention level or control area without intervention; 1.0 minus relative reduction of measure e.g. BI.** **RE of 0 indicates elimination of vector population or dengue incidence**, and relative reduction >1.0 indicates an increase in corresponding measure in the targeted area. RE <1.0 indicates a reduction caused by the intervention compared to control or pre-intervention phase. Meta analysis done						**measured by CI (8 studies)** • Pool RE =0.17(95%CI 0.02,1.28) measured by HI (9 studies) • **Pool RE =0.33 (95%CI 0.30,0.79) measured by BI (11 studies)** **Size of population covered and duration** - The smallest number of people covered with intervention was control using biological methods (median population size of 200, range 20 - 2500) - Integrated vector management focused on larger population (median population size of 12,450; range 210 – 9,600,000) - The shortest duration: chemical intervention applying water treatment (2.5months), and the longest: IVM using EM combined with biological control (20.5months) - Duration of intervention for IVM ranged from 12 months to 20.5 months **Author conclusion** Dengue vector control is effective in reducing vector population, particularly when intervention use a community based, integrated approach which is tailored to local eco-epidemiological and sociocultural settings, and combined with educational programmes to increase knowledge and understanding of best practice. New research should assess the density-dependant effectiveness of each control measure in order to estimate whether reducing vector numbers has an impact on dengue transmission when populations are at critical threshold.	

<table>
<tr><th>Bibliographic citation</th><th>Study Type / Methods</th><th>LE</th><th>Number of patients and patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow up (if applicable)</th><th>Outcome measures/ Effect size</th><th>General comments</th></tr>
<tr><td></td><td>where at least 5 studies with same outcome measures identified.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>3. Alvarado-Castro V, Paredes-Solis S, Nava-Aguilera E, et al. Assessing the effects of interventions for Aedes aegypti control: systematic review and meta analysis of cluster randomised controlled trials. BMC Public Health 2017;17(1):384. Doi 10.1186/S12889-017-4290z

Acapulco University, Mexico</td><td>Systematic review and meta analysis of cluster RCT

Objective:
To review the effectiveness of interventions for dengue vector control, using standard entomological indices as measured in cluster randomised controlled trials (CRCTs).

Method:
Systematic search of Medline, Ovid, BVS, LILACS, ARTEMISA, MBIOMED and MEDIGRAPHIC databases identified CRCTs of interventions to control Aedes aegypti published between Jan 2003 and Oct 2016.
Eligible studies: CRCT of chemical or biological control measures, or community mobilisation, alone or combination; with entomological indices as an endpoint (at least one of three indices; HI, CI and BI. HI: household with larvae or pupae as a proportion of household examined; CI: containers with larvae or pupae as a proportion of containers examined; BI:</td><td>I</td><td>n=18 (in SR) covered 246 intervention clusters (48,131 intervention household) and 288 control clusters (69,430 control household)
in 13 countries: India, Thailand, Sri lanka, Cuba, Haiti, Mexico, Guatemala, Nicaragua, Venezuela, Brazil, Uruguay, Ecuador and Colombia

n=10 (in meta analysis)</td><td>Chemical control (8), biological control (1), community mobilisation for dengue prevention (9)

Chemical: temephos, insecticide treated window and door screens or curtain, treated bed nets, deltamethrin lethal ovitraps and Bti, deltamethrin treated window curtain and container cover

Biological: copepods or Bti</td><td>Routine dengue control activity</td><td>Ranges from 6 weeks to 18 months</td><td>Entomological indices (SR)
- Lower entomological indices in intervention group (for community mobilization), in 4 of 9 CRCTs, overall impact varies but broadly positive with significant impact on at least one index
- Significant impact on pupae per person index at all time point; and HI,CI and BI at baseline in intervention than control (for Biological control, 1 CRCT)
- Impact varied widely (for Chemical control, 8 CRCTs)

Overall Intervention effectiveness (pool):
<table><tr><th>Intervention</th><th>RD (95%CI)</th></tr><tr><td colspan="2">Community mobilisation (n=4)</td></tr><tr><td>• HI</td><td>-0.10(95%CI -0.20,0.00)</td></tr><tr><td>• CI</td><td>-0.03(95%CI -0.05, -0.01)</td></tr><tr><td>• BI</td><td>-0.13(95%CI -0.22, -0.05)</td></tr><tr><td>Biological (n=1)</td><td></td></tr><tr><td>• HI</td><td>-0.02 (95%CI -0.07,0.03)</td></tr><tr><td>• CI</td><td>-0.02 (95%CI -0.04,-0.01)</td></tr><tr><td>• BI</td><td>-0.08 (95%CI -0.15,-0.01)</td></tr><tr><td>Chemical (n=5)</td><td></td></tr><tr><td>• HI</td><td>-0.01 (95%CI -0.05,-0.03)</td></tr><tr><td>• CI</td><td>0.01 (95%CI -0.01,0.02)</td></tr><tr><td>• BI</td><td>0.01 (95%CI -0.03,0.05)</td></tr></table>
Community mobilisation was consistently effective in reducing entomological indices, compared to chemical control.</td><td>Intervention assessed – chemical, biological or community mobilisation</td></tr>
</table>

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	containers with larvae or pupae. Methodological validity assessed using Cochrane risk of bias tool. Meta analysis using random effect model assessed the impact on HI, CI and BI. Intervention effectiveness measured as difference (**overall risk difference)** between intervention and control group at the last point of measurement, for each intervention (chemical, biological, community mobilisation).			Community mobilisation & participation : engagement of local stakeholders, involvement of community in prevention & dissemination, household visits, educational programmes at household & community level, partnership with local services, effort to improve local services)			**Author conclusion** Government that relies on chemical control of Aedes aegypti should consider adding community mobilisation to their prevention efforts. More well conducted CRCTs of complex interventions, including those with biological control, are needed to provide evidence of real impact. Trials of all interventions should measure impact on dengue risk.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
4. Al-Muhandis N, Hunter PR. The value of educational messages embedded in a community-based approach to combat dengue fever: a systematic review and meta analysis. PLoS Negl Trop Dis 2011;5(8):e1278. doi:10.1371/journal.pntd.0001278 University of East Anglia, Norwich, UK	Systematic review **Objective:** To investigate the relative effectiveness (RE) of different educational messages embedded in a community-based approach on the incidence of *Aedes aegypti* larvae using entomological measures as outcomes **Method:** Systematic search using Medline, Embase, Web of Science, Cochrane Library done up to March 2010. Primary outcome: entomological measures; BI specifies the number of containers with Aedes sp larvae per 100 houses, CI represents percentage of water container positive for *aedes sp* larvae, and HI gives percentage of houses with water containers holding immature Aedes spp. Primary effect measure was **relative effectiveness (RE); ratio between entomological index in intervention and control group** (the more effective the intervention, the lower the RE).	I	Included studies=22 South America (11),South East Asia (9), Fiji & French Polynesia (2); Earliest 1967, latest 2009	Educational messages (vary whether or not intervention communities received other intervention) alongside a standard control programme Types: Educational and chemical intervention (9), Educational and other than chemical control (8)	-		• **Correlation of different entomological indices** Pearson correlation coefficient for the RE from the three entomological indices showed high correlation between them; - CI-HI:0.97 - BI-CI: 0.68 - BI-HI:0.66 They concluded that combining the different entomological indices was valid. • **Performance of educational, chemical and other interventions against dengue vector outcome measure:** Pool RE = 0.25(95%CI 0.17,0.37) *(Heterogeneity, Cochran's Q=1254, p<0.001)* Meta regression (exploration of heterogeneity): 60% of between study variance could be explained by: - Whether or not studies used historic/contemporary control - Time from intervention to assessment **Author conclusion** The results suggest that such measures do appear to be effective at reducing entomological indices. With the current evidence available, it is not possible to say what type of educational modalities are the most effective. There is a need to reassess whether other intervention add any further value to educational interventions**.**	Meta analysis is of combined entomological parameter RE = risk ratio

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	Included studies: only study with educational element to their intervention, defined as any community based intervention that had element where members of public were given information intended to change behavior. Inclusion criteria: control of dengue, investigate effect of educational intervention alongside other control approach, quantitative outcomes, community based.							
5. Lima EP, Goulart MOF & Neto MLR. Meta-analysis of studies on chemical, physical and biological agents in the control of *Aedes aegypti.* BMC Public Health 2015;15:858.DOI 10.1186/s12889-015-2199-y Federal University of Cariri, Brazil	Systematic review with meta analysis **Objective** To identify the most effective vector control strategies and the factors that contributed to the success or failure of each strategy. **Method** Systematic search were done from 12 databases from 1974 to December 2013. Intervention: use of any chemical, physical, biological or integrated action against *A aegypti*, regardless of the formula, concentration, form of		Included studies, n=26 from 15 countries Cluster randomized control trial (6), non randomized controlled trial (16), pre-post intervention (4) (Cambodia, Vietnam, Thailand, Pakistan, India, Sri Lanka, Australia, US, Argentina, Brazil, Colombia, Honduras, Guatemala, Colombia, Haiti, Mexico)	Biological (5) Chemical (5) Mechanical (3), integrated strategies (13) Time interval of intervention =2 weeks to 72 months	-	72 months	**Biological control (type):** Fish (3 species), crustaceans, aquatic insects, bacteria based larvicide (Bacillus thuringiensis vas israelensis (Bti)) **Chemical control (type):** Pyrethroids, organophospates, benzoylureas, phenyl ether, thioridazine **Physical/mechanical control (type):** Regular cleaning of containers, container covers and collecting eggs in ovitraps) **Integrated strategies (type):** Physical control, community participation (education, elimination of breeding sites), chemical or biological insecticides added to ovitrap, or impregnated in curtains, bednets or covers	No risk of bias/quality assessment. Methodology of SR followed not documented e.g. PRISMA

<table>
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<tr><td></td><td>application, target stage of the mosquito and duration of treatment. Studies on control strategies that did not include field testing and exclusively on entomological surveillance were excluded.

Meta analysis of studies done using p-value application (programme Bio-Stat 5.0), the p-value for each study was converted into Naperian logarithm and the test applied for obtaining the combined value.</td><td></td><td></td><td></td><td></td><td></td><td>Performance analysis of control strategies (n=22)

<table><tr><th>Statistics</th><th>Biological</th><th>Chemical</th><th>Integrated</th><th>Global</th></tr><tr><td>N</td><td>5</td><td>5</td><td>12</td><td>22</td></tr><tr><td>Chi-square</td><td>72.507</td><td>52.270</td><td>140.035</td><td>277.339</td></tr><tr><td>p</td><td><0.0001</td><td><0.0001</td><td><0.0001</td><td><0.0001</td></tr></table>- All category of intervention contributed significantly to the control of A aegypti (p<0.0001), with integrated intervention showed the greatest impact
- Chemical control alone showed the least performance

Author conclusion
The most effective method was the integrated approach, considering the influence of eco-bio-social determinants in the virus-vector-man epidemiological chain, and community involvement, starting with community empowerment as active agents of vector control.</td><td></td></tr>
<tr><td>6. Gurtler RE, Garelli EF, Coto HD. Effects of a 5-year intervention program to control aedes aegypti and prevent dengue outbreaks in Northern Argentina. PLoS Negl Trop Dis 2009. 3(4):e427.doi:10.1371/journal.pntd.0000427</td><td>Cohort

Objective
To describe the implemented intervention programme and assess long term effect of vector suppressive action on Aedes aegypti indices and incidence of dengue during the 5-year period.

Method
Based on a before-and-after citywide assessment of Aedes aegypti larval indices and the reported</td><td>II-2</td><td>Total houses visited = 168,603, inspected = 120,967
(5 years, 2003-2007)

Baseline houses inspected = 1808 (2002)</td><td>Focal treatment with larvicides of every mosquito developmental site every four months (14 cycles in 5 years,2003-2007), combined with source reduction and ultra-low-volume</td><td>-</td><td>5 years</td><td>Implemented intervention
- Total households treated with larvicide = 37,000 (22.2%, SD: 2.8%) (5-years)
- Kilograms of temephos applied at each focal cycle = mean 193kg (SD 45)
- Total number of positive containers detected at each focal cycle = mean 738 (SD 418)
- Average household inspection per cycle = 8,511

Entomological indices
- HI declined sharply from 13.7% (baseline) to 3.7% (second cycle)
- BI declined from 19.0(baseline) to 4.8(second cycle)
- The indices fluctuated and peaked between summer, with variation between neighbourhood
- Larval indices decreased more sharply immediately after the control action executed at</td><td></td></tr>
</table>

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
(Argentina)	incidence of dengue in Clorinda, northeastern Argentina over 2003-2007. Intervention was focal treatment with larvicides of every mosquito developmental site every four months (14 cycles), combined with source reduction and ultra-low-volume insecticide spraying during emergency operation. Desired control program target: HI<1% and BI <5. Preliminary survey done to establish infestation level (container inspection, emptied disposable containers, larviciding with 1% temephos in sand granules at 1mg per litre or with Bacillus thuringiensis israelensis BTi,VectobacR), of 1,808 random occupied houses (in 2002). A total of 14 cycles of focal treatment conducted at 4-months interval (2003-2007). Educational efforts conducted in schools. Evaluation survey done among those conducting regular control, assessing impact of larviciding shortly after in a convenience sample of blocks.			insecticide spraying (Chemical, physical, education)			cycle 1, than at subsequent cycles - Monthly HI and BI over the 5-years were highly positively correlated (r=0.96,p<0.001) - BI declined significantly in nearly all focal cycles compared to pre-intervention indices clustered by neighbourhood, after allowing for lagged effects of temperature and rainfall, baseline BI and surveillance coverage (multiple regression model) - Larval indices seldom fall to 0 shortly after intervention at the same infested unit (after focal cycle 1 to 7) **Infestation of water holding container type** - Differed largely among types of container - Tanks, barrels, drums for water storage were the most abundant and infested (cycle 12) - Disposable cans, bottles, plastic : second most abundant **Incidence of dengue** Incidence of dengue cases declined from 10.4 per 10,000 in 2000(by DEN-1, 46 confirmed cases and 500 suspect cases) to 0 from 2001 to 2006, then rose to 4.5 cases per 10,000 in 2007(by DEN-3). **Author conclusion**: Control intervention exerted significant effect on larval indices , but failed to keep them below target level during every summer, and achieved sustained community acceptance. For further improvement, a shift is needed towards a multifaceted program with intensified coverage and source reduction efforts, lids or insecticide-treated covers to water storage containers, and a broad social participation aiming at long term sustainability.	

<table>
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<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr>
<td>7. Caprara A, Lima JWO, Pioxoto ACR et al. Entomological impact and social participation in dengue control: a cluster randomized trial Fortaleza, Brazil. Trans R Soc Trop Med Hyg. 2015;109:99-105

(Brazil)</td>
<td>Cluster randomised controlled trial

Objective
• To implement a novel intervention strategy in Brazil using an ecohealth approach
• To analyse its effectiveness and costs in reducing Aedes aegypti vector density as well as its acceptance, feasibility and sustainability

Methods
10 randomly selected intervention cluster with 10 control clusters (using geographically sampling method).

Pre-intervention entomological survey was conducted in November and December 2012. Intervention was developed from January to April 2013 and entomological survey was carried out in May 2013 during post intervention period.

Interventions:</td>
<td>I</td>
<td>10 intervention cluster, 10 control cluster</td>
<td>a)Community workshop

b)involvement of community during clean-up campaign

c)mobilising school children and elderly regarding dengue prevention

d)distribution of information, education and communication (IEC) materials</td>
<td>Routine vector control</td>
<td></td>
<td>Vector breeding places
• All large tanks in intervention cluster were covered at the end of the study (2013)
<table>
<tr><td>Total cluster</td><td>10</td></tr>
<tr><td>Total water tank</td><td>628</td></tr>
<tr><td>Covered water tank</td><td>535</td></tr>
<tr><td>Tanks covered by eco-bio-social project</td><td>93</td></tr>
</table>

Cost
• Total costs of intervention: US$18.89/house
• Costs related to ecohealth intervention: US$2.23/house
• Staff cost : 11 EDAs US$185/ month, 1 field coordinator US$277/month

Vector density
• A total of 2411 places were visited in both dry and rainy season (2353 household and 58 public space)
• HI, CI, BI and PPI increased from the dry season (before intervention) to the rainy season (after the intervention)
• The increase significantly higher in the control area as shown below:</td>
<td></td>
</tr>
</table>

Table 4. Entomological indices in the intervention and control areas, in the dry and rainy season, achieved by the eco-bio-social integrated intervention to control *Aedes aegypti* in Fortaleza, Ceara state, Brazil, 2013

Indicators	Dry season		Rainy season		p-value
	Control	Intervention	Control	Intervention	
House index (%)	0.8383	1.2944	3.1664	2.0497	0.029
Container index	0.1625	0.1799	0.7157	0.2228	0.020
Breteau index	1.0278	1.5991	4.3158	2.4646	0.014
Pupae per	0.0104	0.0229	0.0539	0.0292	0.023

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	a)Community workshop b)involvement of community during clean-up campaign c)mobilizing school children and elderly regarding dengue prevention d)distribution of information, education and communication (IEC) materials The variation of the house index (HI), container index (CI), Breteau Index (BI) and pupae per person (PPI) (i.e; larval indices) from the dry season (before intervention) to the rainy season (after the intervention) was assessed by means of linear mixed models. Qualitative data were recorded, transcribed and transferred to a central database. Cost items were classified according to the resources consumed (personnel, consumables, transport operating cost and other cost incurred in meetings with community), descriptively analysed and aggregated to calculate total costs and costs per						**Empowerment of community (qualitative)** • Leadership (cluster 3 had highest level of leadership, cluster 6 lowest level of leadership) • There were differences in terms of social participation, commitment and leadership capacity in the clusters **Authors' conclusion** Embedding social participation and environmental management for improved dengue vector control was feasible and significantly reduced vector densities. Such a participatory ecohealth approach offers a promising alternative to routine vector control measures.	

<table>
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<tr><td></td><td>house reached.</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>8. Mitchell-Foster K, Ayala EB, Breilh J et al. Integrating participatory community mobilization process to improve dengue prevention: an eco-bio-social scaling up of local successs in Machala, Ecuador. Trans R Soc Trop Med Hyg.2015;109:126-133

Canada</td><td>Cluster randomised controlled trial

Objective
• To examine the effectiveness of applying an integrated community-based approach, comparing with government programs
• To investigate effectiveness and feasibility of scaling up an ecosystem approach to dengue prevention and control

Methods
An integrated intervention strategy (IIS) for dengue prevention (elementary school-based dengue education programme, and clean patio and safe container programme) was implemented in 10 intervention clusters from November 2012 to November 2013 in Machala

Two stage sampling design using satellite image map generated by Google map was used to determine the study clusters

Existing dengue prevention</td><td>I</td><td>20 cluster RCT (10 intervention, 10 control)

1986 household (4014 intervention residents, 3886 control residents)</td><td>Eco-bio-social (integrated community based):

1.Dengue elementary school education (DESE) program

2.Clean patio and safe container (CPSC) programme</td><td>National Vector Borne Disease Control Service (SNEM), MoH

1.Insecticide- based programme

2.Biolarvicide-based programme</td><td>12 months</td><td>PPI value:
• No significant different in PPI at baseline between intervention an control clusters
• IIS significantly reduced overall PPI values in intervention cluster compared to control cluster (Table 1)

Table 1: Study result by treatment using pupa person index (PPI)
<table>
<tr><th>Item</th><th>PPI (2012)</th><th>PPI(2013)</th><th>% Change</th><th>P value</th><th>Person</th><th>Pupa 2012</th><th>Pupa 2013</th></tr>
<tr><td>Total</td><td>0.668</td><td>0.252</td><td>-62.3%</td><td><0.001</td><td>7900</td><td>5278</td><td>1988</td></tr>
<tr><td>Intervention</td><td>0.524</td><td>0.080</td><td>-85.1%</td><td>**</td><td>4014</td><td>2102</td><td>314</td></tr>
<tr><td>Control</td><td>0.817</td><td>0.353</td><td>-47.2%</td><td></td><td>3886</td><td>3176</td><td>1674</td></tr>
</table>
** statistically significant

Effect on PPI pre- and post-intervention
• No significant different in the potential effect of intervention in all clusters (equivalent impact).
• There was greater potential effect in the intervention cluster [adjusted OR=2.2, (95% CI : 1.2, 4.7), p=0.015] compared to control
<table>
<tr><th>Effect</th><th>Odds ratio</th><th>95% CI</th><th>p value</th></tr>
<tr><td colspan="4">All cluster pairs (10 pairs)</td></tr>
<tr><td>Intervention</td><td>1.7</td><td>0.9, 3.3</td><td>0.0121</td></tr>
<tr><td>Biolarviciding</td><td>0.4</td><td>0.1,1.2</td><td>0.091</td></tr>
<tr><td colspan="4">Adjusted (6 cluster pairs)</td></tr>
<tr><td>Intervention</td><td>2.2</td><td>1.2,4.7</td><td>0.015</td></tr>
<tr><td>Biolarviciding</td><td>0.5</td><td>0.1,1.7</td><td>0.286</td></tr>
</table></td><td></td></tr>
</table>

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	programmes served as control treatment Main outcome measured was Pupa per person index (PPI). Other outcome measures were House Index (HI), Breteaux Index (BI) Social mobilization and empowerment with IIS was monitored Pre-intervention baseline surveys were done in March 2012 and post-intervention surveys done in November 2013 (both rainy season) Comparative analysis for RCCT were based on data collected through the use of both entomological and household surveys						**DESE programme** • Of the 10 intervention cluster, 230 children participated in DESE • Reduction in both HI (13.0 % versus 1.3%) and BI (29.6% versus 1.7%) for pre-intervention and post-intervention observed respectively in their household **CPSC programme** • Of the 8 intervention cluster,729 households participated in CPSC • 5 clusters carried out CPSC independently • 3 clusters used capacity building support and human resources from vector control staff **Authors' conclusion:** In the rapidly evolving political climate for dengue control in Equador, integration of successful social mobilization and empowerment strategies with existing and emerging biolarvicide-based government dengue prevention and control programmes is promising in reducing PPI and dengue transmission risk in southern coastal communities like Machala. However, more profound analysis of social determination of healthy is called for to assess sustainability prospects	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
9. Kay BH, Hanh TTT, Le NH et al. Sustainibility and cost of a community-based strategy against aedes aegypti in Northen and central Vietnam. A. J. Trop. Med Hyg.2010;822-830	Cross sectional and cost analysis **Objective** -To see whether or not the community-based dengue control programme represent effective long term solution for the prevention of dengue -To evaluate if the 1998-2000 program was still being maintained 7 years later in 2007 **Methods** Previously, a new community-based mosquito control that resulted in the elimination of *Aedes aegypti* in 40 of 46 communes in northern and central Vietnam was reported During 2007 and 2008, Nam Dinh and Khanh Hoa province in Northern and Central Vietnam, respectively were revisited Nothern Vietnam: • North project commune (NPC) • North extended commune (NEC) • North control commune	III	46 communes in northern and central Vietnam (Northern = 62,563 population, central=11,110 population)	Community based strategy consisted of: - combined vertical & horizontal approach, prioritised control according to larval productivity of major habitat, use of predacious copepods *(Mesocyclops)*, use of communal activities of health collaborators, students, public	-	-	**Program cost** • The recurrent annual cost at Northern - NPC was VND 40 million (6,134 international dollars) with an additional 10% used for start-up costs incurred in the first year. • Recurrent annual project costs ranged from 0.28 international dollars per person at Central - CPC to: 0.61 international dollars per person (in NPC) and 0.89 international dollars per person (in NEC). **Sustainability assessment for northern Vietnam** • Sustainability criteria were summarized for northern commune (NPC and NEC were benchmarked against NCC): ➢ Health benefits were maintained (new DF cases, entomological indices, number of container for Aedes, KAP of householders) ➢ The presence of new dengue cases did not provide useful data on programme efficacy as dengue is sporadic in the north ➢ KAP was higher in NPC and NEC compared to NCC with respect to importance of collecting discarded item and inoculating Mesocyclops ➢ Project activities were best delivered by NPC and NEC compared to NCC ➢ Long term capacity building was strongly maintained in NPC and NEC compared to NCC **Sustainability assessment for central Vietnam** • Sustainability criteria were summarized for central commune (CPC and CEC were benchmarked against CCC): ➢ Health benefit were superior in CPC compared to CCC ➢ General knowledge of dengue was higher	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	Central Vietnam • Central project commune (CPC) • Central extended commune (NEC) • Central control commune (CCC) Previously published sustainability framework was used to compare 13 criteria from Tho Nghiep commune in Nam Dinh (Northern Vietnam) where the local community had adopted the community-based project model using Mesocyclops from 2001 The data were compared against a formal project commune, Xuan Phong (successful intervention activities ceased in 2000) and 4 communes operating under the National Dengue Control programme with data available In Khanh Hoa (Central Vietnam) province, the 2008 data at Ninh Xuan commune (project completion in 2003) were compared with untreated control (Ninh Binh), where few control activities had been undertaken and used						at CPC than CCC (χ^2 = 12.82; P < 0.001) ➢ In terms of dengue vector-control practices in the communes, the proportion of householders who reported cleaning water containers and removing discarded containers as larval control methods did not differ significantly in CPC 4.5 years after project completion (χ^2 = 0.004; P = 0.95), but there was a significant reduction in the proportion of participants that continued to introduce Mesocyclops (78.5% versus 21.2%) ➢ Long-term capacity building at CPC was not as strong as at NPC and NEC **Overall summary of sustainability rating** • At NPC, there was only one disparity in the ratings given by the two researchers, which resulted in sustainability scores of 4.38 and 4.46 of 5.00 (mean = 4.42) • Small differences in 6 of 13 scores for NEC resulted in sustainability scores of 3.92 and 3.46 of 5.00 (mean = 3.69), whereas the rating for CPC was 4.20 • This resulted in well sustained classifications for all communes **Authors conclusion** The three communes where the above community-based strategy had been adopted were rated as well-sustained with annual recurrent total costs (direct and indirect) of \$0.28–0.89 international dollars per person.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	as benchmark Data analysis All statistical analysis were completed using stata 8.0 Outcome: -KAP and household surveys - Sustainability score level of sustainability was scored using a standard five-interval rating system (1–1.5 = regressive, 1.5–2.5 = not sustained, 2.5–3.5 = moderately sustained, 3.5–4.5 = well-sustained, and 4.5–5 = highly sustained -Program costs Direct costs included stipends for collaborators and commune-management committees and supplies for schools and collaborators, whereas other funds were expended by national (mainly in the first year) and provincial health authorities for monitoring and evaluation and for clean-up campaigns. All costs were calculated in Vietnamese Dong (VND), but also reported in internal dollar according to the 2007							

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	purchasing power parities conversion rate (1 int dollar =6,520 VND)							
10. Kittayapong P, Thongyuan S, Olanratmanee P et al. Application of eco-friendly tools and eco-bio-social strategies to control dengue vectors in urban and peri-urban settings in Thailand. Pathog Glob Health. 2012;106(8):446-454. Thailand	Cluster RCT **Objective:** To demonstrate an application of integrated, community-based, eco-bio-social strategies in combination with locally-produced eco-friendly vector control tools in the dengue control programme, emphasizing urban and peri-urban settings in eastern Thailand. **Method:** Three different community settings were selected and were randomly assigned to intervention and control clusters. Key community leaders and relevant governmental authorities were approached to participate in this intervention programme. Ecohealth volunteers were identified and trained in each study community. They were selected among active community health volunteers and were trained by public health experts to conduct vector control activities in their	I	Intervention cluster: 441 household Pupae per person Index: 0.37 Control cluster: - 448 household - Pupae per person Index: 0.38	1) Community participation and health education 2) Dengue Vector Control: -*Bacillus thuringiensis* subsp. israelensis (Bti)and *Mesocyclops thermocyclopoides* (copepods) -Screen net covers (MosNEt®) -Mosquito Traps (Mos House®) -Portable vacuum aspirator (MosCatch ™)	Routine vector control measure using abate (temephos) in potential breeding area and fogging to kill adult mosquito	6 months	**Entomological indices** • At the **six-month** follow-up, entomological indices **decreased in all clusters**. Larval indices (HI, BI and CI), in both treatment and control clusters were **significantly lower** than at baseline. There were no significant differences in HI, CI and BI indices between treatment and control clusters at each surveyed interval. Table: Control measures applied to potential breeding containers and follow-up entomological survey in the treatment (T) and control (C) clusters.	

Items	Baseline T	Baseline C	Month 2 follow-up T	Month 2 follow-up C	Month 4 follow-up T	Month 4 follow-up C	Month 6 follow-up T	Month 6 follow-up C
No. of inspected houses	441	448	403	400	332	368	368	335
No. of inspected containers	3,922	3,173	3,572	2,826	2,610	2,341	2,992	2,011
No. of pupa-positive containers	122	109	66	122	31	50	32	43
No. of pupae	648	583	245	970	60	346	42	361
No. of residents	1,758	1,535	1,565	1,535	1,215	1,457	1,485	1,290
House Index (HI)*	37.19	38.84	33.25	32.00	20.41	21.20	11.68	14.03
Container Index (CI)**	9.20	11.19	8.03	9.24	6.30	5.51	3.01	5.38
Breteau Index (BI)***	81.86	78.79	71.22	65.25	49.10	35.05	24.46	21.49
No. of containers applied Bti sacs	1,969		921		522		588	
No. of containers applied copepods	–		347		168		253	
No. of screen net covers applied on containers	943		–		–		–	

*At the six-month follow-up, the HI in both treatment and control clusters was significantly lower than at baseline, $P=0.000$.
** At the six-month follow-up, the CI in both treatment and control clusters was significantly lower than at baseline, $P=0.002$ and $P=0.001$, respectively.
*** At the six-month follow-up, the BI in both treatment and control clusters was significantly lower than at baseline, $P=0.002$ and $P=0.001$, respectively.

vs. 52.1%, p=0.006) agreed that applying copepods and Bti to water-holding containers was not complicated.

• The percentage of people in the treatment clusters who **agreed that it was only health volunteers who were responsible** for dengue prevention in

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	own communities using environmental management in combination with eco-friendly vector control tools. These trained ecohealth volunteers carried out outreach health education and vector control during household visits. Management of public spaces and public properties, especially solid waste management, was efficiently carried out by local municipalities. Entomological surveys were conducted before the intervention and every two months after (May to Nov 2010). Significant reduction in the pupae per person index in the intervention clusters when compared to the control ones was used as a proxy to determine the impact of this programme.						the community was significantly lower than in the control clusters (12.9% vs. 26.1%, p=0.013). **Author's conclusion:** An eco-friendly dengue vector control programme was successfully implemented in urban and peri-urban settings in Thailand, through intersectoral collaboration and practical action at household level, with a significant reduction in vector densities.	

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<tr><td>11. Kittayapong P, Yoksan S, Chansang U et al. Suppression of dengue transmission by application of Integrated Vector Control Strategies at Sero-positive GIS-based Foci. Am J Trop Med Hyg. 2008;78(1):70-76.

Thailand</td><td>Pre and post-intervention study

Objective:
To report a strategy for integrated, community-based dengue control intervention suitable for semi-rural and rural Thailand that could successfully dengue transmission in a targeted community.

Method:
A serological survey of primary school children from six schools in Chachoengsao Province, Thailand, was performed at the end of the peak of dengue transmission. Geographic Information System (GIS) analysis of sero-positive cases was carried out to determine transmission foci for targeting control implementation.

Vector control implementation was conducted in the foci and also within 100 meters around the foci in the treated areas by community participation in collaboration with the local government.</td><td>II-3</td><td>Six local school (approximately 1800 students, ranging from kindergarten to grade 12)</td><td>Integrated community based intervention consisted of:
1) Source reduction; Clean-up campaign followed by weekly garbage pick-up

2) Screen covers for water jars

3) A combination of Bacillus thuringiensis subsp. israelensis and Mesocyclops thermocyclopoides for various permanent containers other than water jar

4) Permethrin-</td><td>Control – Untreated areas in Wang Yen Subdistrict</td><td>2 years</td><td><u>GIS mapping of dengue foci and Aedes-positive containers</u>
• When compared between first-year and the second-year serological results, the overall IgG and IgM positive rates were 1.85% (30/1625) and 6.72% (118/1755), respectively.
• For the treated community, the average number of positive containers per house with 95% CI in the dengue foci was 4.45±0.33 (3.79-5.10) and out of dengue foci was 2.51±0.27 (1.97-3.04), which was significantly different (t=-3.493, p=0.001, df=150).

<u>Entomological, serological and clinical monitoring</u>
• There was a reduction in the number of Aedes-positive containers and significant reduction in the number of Aedes mosquito in the treated areas after the application of these vector control strategies.
• The proportion of IgG-IgM positive students in the treated areas reduced from 13.46% (first year) to 0% (second year), whereas those from untreated areas increased from 9.43% to 19.15%.

<table><tr><th>Group</th><th colspan="2">Serological</th><th colspan="2">Clinical</th></tr><tr><th></th><th colspan="2">%IgG-IgM+ve (n)</th><th colspan="2">No.+ve cases/100,000 pop</th></tr><tr><th></th><th>Yr1 treated</th><th>Yr2 UT</th><th>Yr1 treated</th><th>Yr2 UT</th></tr><tr><td>Treated</td><td>13.5(83)</td><td>0.0(98)</td><td>265.3</td><td>0.0</td></tr><tr><td>UT</td><td>9.4(66)</td><td>19.2(69)</td><td>217.9</td><td>322.2</td></tr></table>UT = untreated

• There were no dengue cases reported in the treated areas whereas reported cases increased in the untreated areas when compared between the years before (217.9/100,000) and after (322.2/100,000) intervention.</td><td></td></tr>
</table>

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	Vector control strategies included source reduction together with the use of screen covers, a combination of *Bacillus thuringiensis* subsp. israelensis and *Mesocyclops thermocyclopoides*, and lethal ovitraps. Implementation of vector control strategies in the foci was continued until the end of the rainy season. Vector control effectiveness was monitored using entomological, serological, and clinical parameters.			treated lethal ovitraps			**Author's conclusion:** Results showed a significant reduction of dengue vectors as well as a decrease in sero-positive children and clinical cases in treated areas when compared with untreated areas.	
12. Kittayapong P, Chansang U, Chansang C et al. Community participation and appropriate technologies for dengue vector control at transmission foci in Thailand. J Am Mosq Control Assoc. 2006;22(3):538-546. Thailand	Pre and post intervention study **Objective:** To report a cost-effective successful vector control intervention with emphasis on the integrated biological and physical control methodologies and the community participation approach. **Method:** A community-based dengue vector control trial was conducted at transmission foci in Plaeng	II-3	<u>Larval abundance :</u> • Intervention village - 0 to 889 per house • Control village – 0 to 1418 per house <u>Average number of larvae per house:</u> • Intervention village – 234.56±27.32 • Control village –132.57±17.41	1) Community participation and health education 2) Clean-up campaign followed by weekly garbage pick-up 3) Screen covers for water jars	Control village (outside transmission foci)	71 weeks	**Dengue incidence** • The reported DHF case rates in the treated and untreated villages were 265.25 versus 217.86 per 100,000 population, respectively, in the year **before intervention** compared with **0** versus 322.23 per 100,000 population, respectively**, in the year after intervention.** • The use of 3 types of screen covers (daily drinking jars, utility jars, water-storage jar) could prevent development of immature mosquito vectors up to 100% if they were used properly. • The control efficiency of a combination of copepods and Bti fluctuated the most in small hygiene jars used in bathrooms.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	Yao District, Chachoengsao Province, eastern Thailand. Implementation was done by the local community in collaboration with local administration, public health, and school authorities. The approach combined a source reduction campaign with appropriate vector control technologies applied within the foci (within 100 m around the foci) and also within schools attended by children from the treated areas. Vector management measures by local government included cleanup campaigns before the rainy season followed by a routine garbage pickup during the rainy season. Locally made screen covers for water jars, a combination of local *Bacillus thuringiensis subsp. israelensis* and *Mesocyclops thermocyclopoides* (copepod), and locally			4) A combination of *Bacillus thuringiensis* subsp. israelensis and *Mesocyclops thermocyclopoides* for various permanent containers other than water jar 5) Permethrin-treated lethal ovitraps			• The percentage of ovitraps that contained *Aedes* eggs when traps were first placed among natural breeding sites (66.3%) **decreased from 49.6% after the first application to 10.4% at the termination of the study.** The data show that locally made lethal ovitraps could successfully suppress populations of adult female Ae. aegypti for up to about 1 month without changing the permethrin-impregnated paper strips. **Author's conclusion:** The study shown a significant reduction of dengue vectors and dengue hemorrhagic fever cases in treated areas compared with untreated areas. However, the long-term success of the program and the level of involvement of the communities need to be evaluated over time.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	made lethal ovitraps were technologies used by the community in this campaign. Larval surveys were conducted before and after vector control activities commenced. Larval positive houses and the number of larvae sampled were recorded and integrated into the GIS map.							

Evidence Table : Safety
Question : Is IVM safe for *Aedes* control?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
-	-	-	-	-	-	-	-	

Evidence Table : Cost-effectiveness
Question : Is IVM cost-effective for *Aedes* control?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1. Mendoza-Cano O, Hernandez-Suarez CM, Trujillo X et al. Cost-Effectiveness of the strategies to reduce the incidence of Dengue in Colima, Mexico. Int. J Environ.Res. Public Health. 2017;14 (890); doi:10.3390/ijerph 14080890 (Mexico)	**Study design** Cost-effectiveness analysis **Objective** To evaluate cost-effectiveness analysis of three different strategies: community participation, ULV spraying and the combination of both **Method** A randomised controlled community trial took place from February 2008 to August 2008 in Colima, Mexico Multistage cluster sampling used was: • Grouping the municipalities into three location according to geographical area • Eight clusters were selected (randomly) • 10 houses randomly selected by random procedure Study group (n=4): • **A (community participation)** ➢ Printed material, random group visit, integration of discussion group, game and promotion		4 municipalities, 4 blocks (n=407)	-Community participation -ULV -Community participation + ULV	Neither Community participation nor ULV	7 months	**Direct cost (USD):** • A=27,393.18 • B=31,170.47 • A+B=58,170.47 • C=12,979.26 - Group A (community participation) had the lowest cost when compared with control group - The direct costs from group AB were the highest **Efficiency & effectiveness of vector-control interventions** The incidence of the vector-borne disease was similar between groups B and AB The highest efficiency and effectiveness estimates were observed in group B	

Group	Cases Tested/Positives	Incidence [a]	Incidence Treated by C [b]	Efficiency [c]	Effectiveness [d]
A	23/4	17.4% (12.6–24)	0.58	0.423	6.93
B	175/25	14.3% (9.3–19.3)	0.47	0.526	6.97
AB	146/20	14.4% (9.4–19.2)	0.48	0.523	5.61
C	63/19	30.2% (20–40)	1.00	0	0

Abbreviations: A, community participation; B, ultra-low volume (ULV) nebulization, AB, community participation and ULV fumigation; C, control; [a] The cumulative incidence; [b] Incidence treated by C = Incidence Ratio Treatment/Control; [c] Efficiency = 1-Incidence treated by C; [d] Avoided DALY (Disability-Adjusted Life Year).

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	programme • **B [Ultra-low volume (ULV)]** ➢ Permethrin and pipronyl butoxide (11.1g active ingredient/ hectare) • **AB (Both intervention)** • **Control** ➢ Neither campaign nor ULV Incidence rate were calculated Rate ratio was estimated by means of bivariate logistic regression Primary outcome of interest were: • Dengue cumulative incidence • DALY's avoided Direct cost associated with each intervention were also computed Dengue rates were used to evaluate the efficacy of each intervention using the number of laboratory-confirmed incident cases after the follow-up (seven months) DALY was calculated based on 2008 projections from						However, the cost-effectiveness balance shown that strategy of community participation (A) was more cost-effective ($3952.84 per DALY avoided). Table: Cost-effectiveness balance.	

Group	Costs ($) per DALY [a]
A	3952.84
B	4472.09
AB	10,439.15
C	-

Abbreviations: DALY, Disability-Adjusted Life Year; [a] The direct costs associated with the interventions per DALY avoided are presented.

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							Authors conclusion Our findings suggest that efforts to improve community participation in vector control and ULV-spraying alone are cost-effective and may be useful to reduce the vector density and dengue incidence.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	National Population Council. Cost-effectiveness approach (direct cost/DALYs avoided) was used to evaluate the implemented interventions							
2. Luz PM, Vanni T, Medlock J, et al. Dengue vector control strategies in an urban setting: an economic modeling assessment. Lancet 2011;377(9778):1673-1680.doi:10.1016/S0140-6736(11)60246-8. Rio de Janeiro, Brazil	**Study design** Cost-effectiveness analysis **Objective:** To estimate the effect of different insecticide-based vector control strategies on health and health economic outcomes **Method:** A dengue transmission model was developed, that extends the previous mosquito model to include human population dynamics and dengue transmission. The mosquito model includes seasonality and population genetics of insecticide-resistance evolution. The model parameters were set with ecological and biological data specific to Aedes aegypti. The effect of vector control was assessed for a 5-year period. Health outcomes (dengue burden) were measured using DALYs (DALYs lost). Analysis was done from a societal perspective. Costs were expressed in 2009 USD.		Rio de Janeiro, Brazil (example of a resource-constrained urban setting with endemic dengue)	Two forms of vector control were analysed, adult and larval control; consisted of 1 to 6 applications every year. Combination strategies were also assessed, thus including no vector control, a total of 43 vector control strategies were considered. Larval control persist in environment for 2 months during	No vector control		**Effect on Dengue burden** - For the entire 5-year period, expected dengue burden was 1133 DALYs lost per million populations - Average annual dengue burden was 227 DALYs lost per million population - For the entire 5-year period, 3 applications of high-efficacy **larval control** every year reduced the dengue burden the most; resulting in 829 DALYs lost per million individuals - For the entire 5-year period, 6 applications of high-efficacy **adult control** every year reduced the dengue burden the most; resulting in 248 DALYs lost per million individuals - Of the **combined intervention strategies** during the 5-year period, one high-efficacy larval control application and five low-efficacy adult control applications reduce the dengue burden to the greatest extent; 733 DALYs lost per million individuals - Of **all vector control strategies,** the strategy that most substantially reduce the number of DALYs lost per million population during the 5-year period was 6 applications of high-efficacy adult vector control.	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	Costs and DALYs were discounted at a yearly rate of 3%. CEA estimating incremental cost-effectiveness ratio of all 43 vector control strategies were calculated, including strategies for adult and larval control, at varying efficacies (high, medium and low) and yearly application frequencies (1 to 6 applications). Comparative value was measured in $ per DALY saved during the 5-year vector control assessment period. The Brazil-specific thresholds of $24660 per DALY saved for a cost-effective intervention, and $8220 per DALY saved for a very cost-effective intervention, based on criteria of the WHO Commission of Macroeconomics and Health. Probabilistic sensitivity analysis and threshold analysis were done to examine the effect of parameter uncertainty on the results.			which the effectivenes s wanes, adult control with ULV insecticide has immediate effect lasts for 1 day. A range of efficacies was explored; high efficacy (90% mortality), medium-efficacy (60% mortality) and low efficacy (30% mortality).			**Cost-effectiveness** - 3 strategies were non-dominated; • no control, • use of 2 applications of high-efficacy adult control, • use of 6 applications of high-efficacy adult control - ICER • use of 2 applications of high-efficacy adult control ($615 per DALY saved) • use of 6 applications of high-efficacy adult control ($1267 per DALY saved) • 6 high-efficacy adult vector control application per year has a cost-effectiveness ratio that meet WHO standard for a cost-effective or very cost-effective intervention • Sensitivity analysis showed that if cost of adult control was more than 8.2 times the cost of larval control, then all strategies based on adult control became dominated. **Author's conclusion** Six high-efficacy adult vector control application per year has a cost-effectiveness ratio that meet WHO standard for a cost-effective or very cost-effective intervention. Year-round larval control can be counterproductive, exacerbating epidemics in later years because of evolution of insecticide resistance and loss of herd immunity. Reassessment of vector control policies that are based on larval control only was suggested.	

<table>
<tr><th>Bibliographic citation</th><th>Study Type / Methods</th><th>LE</th><th>Number of patients and patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow up (if applicable)</th><th>Outcome measures/ Effect size</th><th>General comments</th></tr>
<tr>
<td>3. Baly A. Toledo M.E, Boelaert M et al. Cost effectiveness of Aedes aegypti control programmes: participatory versus vertical. Trans R Soc Trop Med Hyg. 2007; 101 (6): 578-586

Cuba</td>
<td>Study design
Cost effectiveness analysis

Objective
To present a cost-effectiveness of two alternative strategies for Aedes aegypti control: a vertical versus a community-based approach

Methods
An economic appraisal was conducted of two strategies for Aedes aegypti control: a vertical versus a community-based approach.

Study site: Santiago de Cuba (470 000 population)

Study was carried out from a number of different perspective : the health system provider, the vertical programme, a community perspective, and the society

Time horizon was 2 years (2001-2002)

Costs were calculated for the period 2000–2002 in three pilot areas of Santiago de Cuba where a community intervention was implemented and compared with three control areas with routine vertical programme activities.

Reduction in A. aegypti foci</td>
<td></td>
<td>470,000 population</td>
<td>Community participation strategy
-Form community working group
-volunteer participatory
-no financial incentives
-members indentify problem and needs, elaborate, implemented and evaluate action plans
-necessary equipment and materials were provided free of charge by local government</td>
<td>Vertical vector control programme
-focal and perifocal larval control
-blanket spraying
-Replace defect water tank
-reduce house inspection
-local leaders training</td>
<td></td>
<td>Total cost

Total cost (US$) of the vertical Ae aegypti control programme in 2000-2002 was US$ 24,395,039 (52 per in habitant)
Economic cost comparing intervention and control areas in 2000-2002

<table>
<tr><td>Input</td><td colspan="2">Intervention</td><td colspan="2">Control</td></tr>
<tr><td></td><td>Baseline</td><td>Total</td><td>Baseline</td><td>Tota</td></tr>
<tr><td>Total cost</td><td>243,746</td><td>692,290</td><td>263,486</td><td>825.09</td></tr>
</table>
Total = 2001-2002

Reduction of foci

Number of A. aegypti foci in the pilot areas and the control areas fell by 459 and 467, respectively.

Cost-effectiveness

The Community-based approach was more cost-effective compared to control from health system perspective (US$964 vs US$ 1406 per focus) as well as from society perspective (US$1508 vs US$1767 per focus)

<table>
<tr><th>Perspective</th><th>Intervention (US$)</th><th>Control (US$)</th><th>Incremental cost per focus eliminated</th></tr>
<tr><td>Health system</td><td>964</td><td>1406</td><td>26775</td></tr>
<tr><td>Vertical programme</td><td>795</td><td>1183</td><td>23481</td></tr>
<tr><td>Community</td><td>1508</td><td>1767</td><td>-10147</td></tr>
<tr><td>Society</td><td>544</td><td>361</td><td>16628</td></tr>
</table>
</td>
<td></td>
</tr>
</table>

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	was chosen as the measure of effectiveness. Economic cost of both strategies were estimated for year 2000 (before intervention), 2001 and 2002 (During implementation)						**Author conclusion:** The described community based intervention for *A aegypti* control when intertwined with the vertical control programme, appears to be the superior strategy. Although entomological indices reported are very low in Cuba, dengue outbreaks have occurred with this level of infestation. These finding could be useful for health decision making in allocating resources for vector control programme in other countries.	
4. Baly A, Toledo ME, Rodriguez K, et al. Costs of dengue prevention and incremental cost of dengue outbreak control in Guantanamo, Cuba. Tropical medicine and International health 2012.17(1);123-132 Cuba	**Cost analysis** **Objective:** To assess the economic cost of routine *Aedes aegypti* control in at risk environment without dengue endemicity and the incremental costs incurred during a sporadic outbreak. **Method:** This study was conducted in 2006, in Guantanamo, east Cuba. Analysis was from societal perspective. Cost incurred in 2006 in dengue control was calculated in months without dengue transmission (January-July) and during an outbreak (August-December) using micro costing method except for the hospital, where macro costing was used to derive the inpatient cost per day for the wards managing dengue cases. Costs were classified		Guantanamo inhabitants =244,100 (68 648 households)	Vector control programme: entomological surveillance, source reduction through periodic inspection of houses, larviciding with temephos in water storage containers, selective perifocal insecticide spraying of adult mosquitoes, health education, enforcement of legislation	-	-	**Cost** - The total economic cost per inhabitant per months increased from USD2.76 in months without transmission to USD6.05 during an outbreak for dengue control and management. - In absolute term, the average monthly cost increased from USD 673959 (in month without transmission) to USD 1 477 617 (during an outbreak); amounted to 0.7% of the country's monthly GDP in period without transmission to 1.5% in the period with transmission - The cost for *Aedes aegypti* vector conrol programme increased from USD1.67 to USD 1.88 per inhabitant per month, or USD 408 281.8 (in month without transmission) to USD 459 406.0 per month (during an outbreak) - Incremental costs during the outbreak were mainly incurred by the population, the primary/secondary level of healthcare system, hardly by vector control programme (USD1.64, USD1.44 and USD0.21 per inhabitant per month	

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	by actor/activity and subsequently as recurrent and capital costs. Recurrent cost included salaries, supplies and materials (insecticide, larvicide, diagnostic test, drugs, protective clothing, glove, office materials), operational cost (fuel & lubricants), vehicle rent, vehicle & building, food and per diem, maintenance of equipment), and utilities (electricity, water, telephone). For capital means (portable fogging equipment, trucks for spatial spraying, laboratory equipment, furniture), their time of use were recorded. Data sources were bookkeeping records, registers, direct observations and semi-structured interviews with health system managers, and randomly selected nurses, family doctors and vector control personnel. All costs were analysed at constant prices and converted at the 2006 official exchange rate of 1peso=0.92USD.						respectively). - In both periods, the main cost drivers for Aedes control programme, the healthcare system and the community were the value of personnel and volunteer time or productivity losses. **Author conclusion** Intensive efforts to keep *A aegypti* infestation low entail important economic costs for society. When a dengue outbreak does occur eventually, costs increase sharply. In-depth studies should assess which mix of activities and actors could maximize the effectiveness and cost-effectiveness of routine *Aedes* control and dengue prevention.	

<table>
<tr><th>Bibliographic citation</th><th>Study Type / Methods</th><th>LE</th><th>Number of patients and patient characteristics</th><th>Intervention</th><th>Comparison</th><th>Length of follow up (if applicable)</th><th>Outcome measures/ Effect size</th><th>General comments</th></tr>
<tr>
<td>5. Packeriasamy PR, Ng CW, Dahlui M, et al. Cost of Dengue Vector Control Activities in Malaysia. Am J Trop Med Hyg 2015. 93(5);1020-1027.

Malaysia</td>
<td>Cost analysis

Objective:
To estimate the cost of the national dengue vector control programme in Malaysia through examination of inputs and costs incurred by public agencies at all levels of the government

Method:
20 study sites comprised of 8 District Health Dept (DHD), 3 State Health Dept, 1 Federal (Vector Borne Disease Control, Disease Control Division) and 8 local authorities in selected DHD participated, sampled using probability proportional to size method.

Bottom-up costing approach was used. All elements of the vector control program was initially identified, following with resource utilization and unit cost of each resource obtained. Information was collected to reflect resource used in 2010. Analysis was done from funder (government) perspective, only direct cost included. Data included capital and recurrent expenditures; annual discount rate of 3% was used for capital cost.

Data from DHD recorded</td>
<td></td>
<td>N=16,676 dengue cases from 8 selected DHD (36.1% of 46,171 cases reported in Malaysia in 2010)</td>
<td>Dengue vector control (nine line items, five functional groups)

Line items (human resources, buildings, vehicles, fogging equipment, pesticides, PPE, outsourced services, National dengue prevention advertisement campaign) and five functional groups (inspection of premises, entomological surveillance, fogging, larviciding, health education</td>
<td>-</td>
<td>-</td>
<td>Cost
- In 2010, Malaysia spent an estimated US$73.5 million (95%CI 62.0, 86.3 million), constituting 0.03% of the country's GDP in 2010 (US$247.5billion) and 1.2% of the total government funding for healthcare in Malaysia (US$6.0billion).

<table>
<tr><th>Total cost</th><th>District</th><th>State</th><th>Fed</th><th>All level</th></tr>
<tr><td>Total (US$Mil)</td><td>67.73 (57.20, 79.85)</td><td>4.00 (3.11, 4.78)</td><td>1.72</td><td>73.45 (62,86)</td></tr>
<tr><td>Per reported case (US$)</td><td>1,467.0 (1239, 1729)</td><td>86.6 ((67.31,103.54)</td><td>37.21</td><td>1590.9 (1343, 1870)</td></tr>
<tr><td>Per capita population (US$)</td><td>2.47 (2.09, 2.91)</td><td>0.15 (0.11, 0.17)</td><td>0.06</td><td>2.68 (2.26, 3.15)</td></tr>
</table>

- 92.2% of these cost was incurred at DHD level
- Human resources costs made up 64.8% of total national vector control costs
- The cost of pesticide amounted to 10.9% of the total cost

District Health Department
- The average district vector control cost was US$1.4 million, ranged from US$0.2million in Sik to US$2.8 million in Gombak.
- DHD with more annual reported dengue cases tended to have more costly vector control expenditures
- Regression equation
DHD cost(US$) = $622,000 + cases x $380 ($R^2$=0.790,p=0.019)
- The main driver for cost in the DHD were for human resources (60.7%), and pesticides (13.6%)</td>
<td></td>
</tr>
</table>

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	using nine line items (human resources, buildings, vehicles, fogging equipment, pesticides, PPE, outsourced services, National dengue prevention advertisement campaign) and five functional groups (inspection of premises, entomological surveillance, fogging, larviciding, health education). Vector control activities at SHD and FHD used only three line items (human resource, building, vehicle with advertisement campaign). Estimates of vector control cost for the district, state and federal level were summed upto provide the estimated national dengue vector control cost for Malaysia in 2010. All costs are reported in US$ using the average 2010 exchange rate (US41 equals to RM3.20).						**State and Federal Health Dept** - The average cost for State Vector Control cost was US$0.3million, ranging from US$0.2million (Malacca) to US$0.3million (Kedah). - The main driver for cost in SHD/FHD was for human resources. **Author conclusion** Malaysia is an upper middle income country that spends annually approximately 5% of total GDP on health overall, and 0.03% specifically on dengue vector control. Dengue poses significant economic burden to the country with a combined annual cost of prevention and illness of US$175.7million. Malaysia has been reliant on a government funded integrated vector control programme which include effort to garner community support through health education activities. This study's quantification of dengue economic burden informs policy makers and stakeholders regarding the implementation of existing and new technologies for controlling dengue.	

Evidence Table : Social
Question : Is IVM accepted for *Aedes* control?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
1.Tana S, Umniyati S, Petzold M et al. Building and analyzing an innovative community-centered dengue-ecosystem management intervention in Yogyakarta, Indonesia. Pathog Glob Health. 2012;106(8):469-478. Indonesia	Pre and post intervention study Objective: To build an innovative community-centered dengue-ecosystem management intervention in the city and to assess the process and results. Method: For describing the baseline situation, entomological surveys and household surveys were carried out in six randomly selected neighborhoods in Yogyakarta city, documents were analyzed and different stakeholders involved in dengue control and environmental management were interviewed. Then a community-centered dengue-ecosystem management intervention was built up in two of the neighborhoods (Demangan and Giwangan) whereas two neighborhoods served as controls with no intervention (Tahunan and Bener). Six months after the intervention follow up		n=6 neighbourhood	• Community involvement and empowerment (meetings, forum, leaders etc) • Involvement of other partner (environmental health forum, local political authorities etc) • Production of intervention tools such as communication materials and development of awareness campaign in school	No intervention	6 months	• At baseline, there's a lack of community involvement and knowledge in dengue control. The community sees dengue control as government responsibility, and has limited knowledge about mosquito breeding places. • Six months after the start of the intervention phase, the entire program (planning, implementation and evaluation) was led by the community with the involvement of women groups. • Post-intervention surveys in the study neighbourhoods showed that respondents were more knowledgeable about dengue and dengue prevention than respondents in the control group: respondents expressing the need for water container management and other vector control measures increased substantially Table 1. Table 1. Knowledge about dengue prevention before and after intervention	

	Before		After		
Suggested actions	Control N=210	Intervention N=213	Control N= 200	Intervention N=201	Difference of difference
Do water container management at home	31.90%	35.01%	27.75%	71.40%	40.54%
Put larvivorous fish into water tanks	4.50%	7.20%	5%	51.70%	44.00%
Put mosquito wire screens on windows and doors	0.50%	2.70%	0.50%	45.80%	43.10%
Put pyriproxifen into the water	26%	28.30%	5.50%	41.30%	33.50%
Spray insecticide in your home	7.50%	6.70%	3%	10.40%	8.20%

Evidence Table : Social
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Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	surveys (household interviews and entomological) were conducted as well as focus group discussions and key informant interviews.						in houses and public spaces were mentioned. The percentage of families who were protecting or destroying breeding places increased in the intervention group (difference of differences = 6.3%).	
2.Wai KT, Htun PT, Oo T et al. Community-centred eco-bio-social approach to control dengue vectors: an intervention study from Myanmar. Pathog Glob Health. 2012;106(8):461-468. Myanmar	Pre and post intervention study Objective: To build up and analyse the feasibility, process, and effectiveness of a partnership-driven ecosystem management intervention in reducing dengue vector breeding and constructing sustainable partnerships among multiple stakeholders. Method: A community-based intervention study was conducted from May 2009 to January 2010 in Yangon city. Six high-risk and six low-risk clusters were randomized and allocated as intervention and routine service areas, respectively. For each cluster, 100 households were covered. Bi-monthly entomological		n=12 clusters	Eco-friendly multi-stakeholder partner groups (Thingaha) and ward-based volunteers, informed decision-making of householders, followed by integrated vector management approach.			<u>Preference</u> • At baseline, there was little collaboration and partnership among stakeholders in dengue vector control and the community was a passive recipient of public health interventions. • The intervention package mainly delivered by Eco-health friendly partner group (EFG) improved the understanding and shared responsibility among local authorities and the community. Distributing pamphlets and booklets and assisting people in the application of targeted container interventions **strengthened the leadership of EFG and the development of sense of ownership by community members**. Combined measures (chemical, mechanical and biological) were most frequently favored (44.8% of cluster dwellers) while chemical measures (pyryproxyfen and Bti) were the second choice (34.2% of cluster dwellers) and mechanical measures (lid covers and cotton net sweepers) the third choice (16.5% of cluster dwellers). Biological measures (dragonfly nymphs) were preferred in a	

Evidence Table : Social
Question : Is IVM accepted for *Aedes* control?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
	evaluations (i.e. larval and pupal surveys) and household acceptability surveys at the end of 6-month intervention period were conducted, supplemented by qualitative evaluations (focus group discussion and in-depth interviews).						combined package but rarely alone. <u>Knowledge, Attitude and Practice</u> • At baseline, the overall knowledge of 2,000 respondents on dengue related issues was high but their container management practices were inadequate especially for productive large size containers. • Qualitative evaluations after the intervention captured that people`s awareness of appropriate vector control options for specific containers was highly improved as well as positive attitudes towards joint actions. • At the end of the intervention period, nearly 45% of cluster dwellers accepted pyriproxyfen alone or in combination with other measures (Table 1). They perceived the chemical as being extremely beneficial and nearly 60% had full confidence in it. Of cluster dwellers using Bti for their ceramic bowls, only 28% perceived it to be extremely beneficial. Lid covers were accepted by 52 households per cluster and 60% of cluster dwellers were fully confident to use them continuously which was important for vector control in the intervention clusters. Dragon fly nymphs were found in 12 households per cluster but nearly 60% of cluster dwellers found those nymphs as being extremely beneficial and perceived them as being important in removal of larvae and	

Evidence Table : Social
Question : Is IVM accepted for *Aedes* control?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							pupae from their water containers. Nearly 42% of cluster dwellers perceived waste collection bags as extremely beneficial for them and 52% was fully confident for continuity in use. There were no differences between high and low risk clusters. The results indicated that people were less enthusiastic about Bti and cotton net sweepers. • In the FGDs and observations following the intervention, it became clear that householders' responsibility in managing dengue vector breeding sites was enhanced. They became interested in the inspection and removal of larvae in their homes; they used lid covers and cotton net sweepers and scrubbed the containers and changed the water regularly in contrast to responses at baseline when household members did not regularly scrubbing and changing water especially of the large containers.	

Evidence Table : Social
Question : Is IVM accepted for *Aedes* control?

Bibliographic citation	Study Type / Methods	LE	Number of patients and patient characteristics	Intervention	Comparison	Length of follow up (if applicable)	Outcome measures/ Effect size	General comments
							Table 1. Acceptability of six intervention tools in intervention clusters	

Cluster dwellers who accepted †	Average ofclusters	% acceptance
Pyriproxyfen		
Very desirable/extremely beneficial	5.17	44.6
Definitely feasible in households	5.17	43.9
Very important	4.67	39.4
Confident	72	59.3
Bti		
Very desirable/extremely beneficial	6	28.0
Definitely feasible in households	6	32.5
Very important	6	28.2
Confident	10	49.2
Lid covers		
Very desirable/extremely beneficial	27	51.6
Definitely feasible in households	26	50.5
Very important	24	46.1
Confident	31	60.5
Cotton-net sweepers		
Very desirable/extremely beneficial	15	32.7
Definitely feasible in households	14	31.2
Very important	14	30.3
Confident	14	30.3
Dragon fly nymphs		
Very desirable/extremely beneficial	7	57.4
Definitely feasible in households	7	59.4
Very important	7	58.0
Confident	8	64.3
Waste collection bags		
Very desirable/extremely beneficial	31	41.9
Definitely feasible in households	29	38.1
Very important	31	41.5
Confident	39	53.0

† Multiple responses; Totals do not add up to 100

Appendix 6

LIST OF EXCLUDED STUDIES

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